SHOCK AND CIRCULATORY HOMEOSTASIS

Transactions of the First Conference
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Edited by
HAROLD D. GREEN, M D
PROFESSOR OF PHYSIOLOGY AND PHARMACOLOGY
BOWMAN GRAY SCHOOL OF MEDICINE
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PARTICIPANTS

First Conference on Shock and Circulatory Homeostasis

MEMBERS

EPHRAIM SHORR, *Chairman*
Department of Medicine, Cornell University Medical College
New York, N Y

HAROLD D GREEN, *Secretary*
Department of Physiology and Pharmacology
Bowman Gray School of Medicine of Wake Forest College
Winston-Salem, N C

STANLEY E BRADLEY
Department of Medicine, College of Physicians & Surgeons, Columbia University
New York, N Y

GEORGE E BURCH
Department of Medicine, School of Medicine, Tulane University
New Orleans, La

ALAN C BURTON
Department of Biophysics, Medical School, University of Western Ontario
London, Ontario, Canada

JACOB FINE
Department of Surgery, Harvard Medical School
Boston, Mass

R E HAIST
Department of Physiology, University of Toronto
Toronto, Ontario, Canada

MELVIN H KNISELY*
Department of Anatomy, Medical College of the State of South Carolina
Charleston, S C

MARK NICKERSON
Department of Pharmacology, School of Medicine, University of Michigan
Ann Arbor, Mich

J PULASKI, LT COL *
Division of Surgery, Armed Forces Research and Graduate School
Washington, D C

JOHN W REMINGTON
Department of Physiology, University of Georgia School of Medicine
Augusta, Ga.

DICKINSON W RICHARDS, JR *
Department of Medicine, College of Physicians & Surgeons, Columbia University
New York, N Y

EWALD E SELKURT
Department of Physiology, School of Medicine, Western Reserve University
Cleveland, Ohio

---

* Absent

EUGENE A STEAD, Jr
Department of Medicine, School of Medicine, Duke University
Durham, N C

BENJAMIN W ZWEIFACH
Department of Medicine, Cornell University Medical College
New York, N Y

GUESTS

K J FRANKLIN
Department of Physiology, Medical College of St Bartholomew's Hospital
London, England

THOMAS J HALEY
Division of Pharmacology & Toxology
Atomic Energy Project, University of California at Los Angeles
Los Angeles, Calif

JOHN M HOWARD, CAPT
Army Medical Service Graduate School, Army Medical Center
Washington, D C

SHEILA HOWARTH
Institute of Cardiology, National Heart Hospital, University of London
London, England

CHESTER HYMAN
Department of Physiology, University of Southern California
Los Angeles, Calif

FRANCIS D MOORE
Department of Surgery, Harvard Medical School
Boston, Mass

RUSSELL M NELSON, LT (MC)
Division of Surgery, Walter Reed Army Medical Center
Washington, D C

ELLIOTT F OSSERMAN, LT, USNR
Naval Medical Research Institute
Bethesda, Md

E P SHARPEY-SCHAFER
Department of Medicine, St Thomas Hospital Medical School
London, England

MARGARET H SLOAN
Division of Medical Sciences, National Research Council
Washington, D C

Josiah Macy, Jr Foundation

FRANK FREMONT-SMITH, *Medical Director*

JANET FREED, *Assistant for the Conference Program*

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First Conference on Shock and Circulatory Homeostasis

JOSIAH MACY, JR. FOUNDATION CONFERENCE PROGRAM

As an introduction to these Transactions of the First Conference on Shock and Circulatory Homeostasis, I should like to outline what it is that the Foundation hopes to accomplish by its Conference Program

We are interested, first of all, in furthering knowledge about shock and circulatory homeostasis, and to this end the participants were brought together to exchange ideas, experiences, data, and methods In addition to this particular goal, however, there is a further, and perhaps more fundamental, aim which is shared by all our conference groups the promotion of meaningful communication between scientific disciplines

The problem of communication between disciplines we feel to be a very real and very urgent one, the most effective advancement of the whole of science being to a large extent dependent upon it Because of the accelerating rate at which new knowledge is accumulating and because discoveries in one field so often result from information gained in quite another, channels must be established for the most relevant dissemination of this knowledge

The increasing realization that nature itself recognizes no boundaries makes it evident also that the continued isolation of the several branches of science is a serious obstacle to scientific progress Particularly is it so in medicine that the limited view through the lens of one discipline is no longer enough For example, today medicine must be well versed in nuclear physics because of the tracer techniques and the injury which can result from radiation At the other extreme, medicine is certainly a social science and, through mental health, must be concerned with economic and social questions The answer, then, is not further fragmentation into increasingly isolated specialties, disciplines, and departments, but the integration of science and scientific knowledge for the enrichment of all branches This integration, we feel, can be encouraged by providing opportunities for a multiprofessional approach to given topics

Although the fertility of the multidiscipline approach is recognized, adequate provision is not made for it by our universities, scientific societies, and journals And perhaps the presence of other

as the painting of a portrait or the composing of a symphony Although logic is, of course, necessary in order to rearrange, to test, and to validate, research thrives on creativity which has its source in unconscious, nonrational processes Unfortunately, however, in the finished products which are presented to the world through research reports this integral part of scientific endeavor is shriveled by the cold, white light of logic By preserving the informality of our conferences in the published transactions, we hope to give a truer picture of what actually goes on in the minds of scientists and of the role which creativity plays.

FRANK FREMONT-SMITH, M. D.,
Medical Director

hindering factors must be admitted. Partly semantic in nature, they may also to some degree be psychological. Admittedly, it is oftentimes difficult to accept data derived from methods with which one is unfamiliar. By making free and informal discussion the central core of our meetings, we hope to achieve an atmosphere which minimizes as much as possible these emotional barriers.

Thus, our meetings are in contrast to the usual scientific gatherings. They are not designed to present neat solutions to tidy problems but to elicit provocative discussion of the difficulties which are being encountered in research and practice. For this reason, we ask that the presentations be relatively brief and that emphasis be placed on discussion as the heart of the meeting. Our hope is that the participants will come prepared not to defend a single point of view but to take advantage of the meeting as an opportunity to speak with representatives of other disciplines in much the same way that they would talk with their own colleagues in their own laboratories.

We have, now, thirteen groups functioning under the Conference Program on the following topics: adrenal cortex, aging, blood clotting, connective tissues, consciousness, cybernetics, infancy and childhood, liver injury, metabolic interrelations, nerve impulse, renal function, cold injury, and shock and circulatory homeostasis.

When a new conference is organized, the Chairman, in consultation with the Foundation, selects fifteen scientists to be the nucleus of the group, and every effort is made to include representatives from all pertinent disciplines. From time to time new members are added by the group to fill gaps in viewpoint or technique. A limited number of guests are invited to attend each meeting, but, for the purpose of promoting full participation by all members and guests, attendance at any meeting is limited to twenty-five. It is inevitable that in no topic can we possibly include more than a small fraction of the key investigators in the field, and one of the difficulties in forming a group like this is that it is necessary to leave out so many people whom we should like to include.

The transactions of these meetings are recorded and published. This is done because the Foundation wishes to make current thinking in a field available to all those working in it, and because it believes that conveying to those in other fields who are concerned with science, for example, government officials, administrators, etc., the essential nature of scientific research is also an important problem in communication. Logic is a vital aspect of science, but equally essential is the intuitive or creative aspect. Research is as creative

INTRODUCTORY REMARKS

EPHRAIM SHORR
Chairman

DURING THE LAST war, when a great deal of work on shock was activated, largely under the influence of the Office of Scientific Research and Development, those of us who worked on projects which were classified as restricted, confidential, or secret felt as if we might be growing to resemble the three monkeys, one of whom saw no evil, another heard no evil, and the last spoke no evil We did not know to whom we might speak, listen, or look

This lack of communication between people working toward a common objective so impressed Dr. Fremont-Smith with its futility that he asked permission to try to establish liaison between the groups by means of a conference on shock. That first meeting of minds took place in New Haven in 1943 and it led to a continued exchange of ideas in the form of Macy Conferences I am sure that those of you who attended the Conferences will agree that it was one of the most provocative measures which could have been taken

Following the end of the war in 1945, there was a waning of activity in the field of shock It is hoped that the present reincarnation of the early Macy Conferences on this problem will stimulate the endeavors which have begun again in response to the present emergency, and I feel certain that the meeting of these minds, during the next five years, cannot help but accelerate the progress of the work in this country and abroad

One of Dr Fremont-Smith's concerns as director of the Macy Foundation's Conference Program is with the emotional aspects of communication This calls to mind that Claude Bernard noted two reactions which result from the inevitable anxiety of people regarding the validity of their own concepts as other concepts impinge upon them One of these reactions is doubt, and that is good, for if we doubt, we then test our doubts The other reaction is skepticism, which is really antiscience for it says, "I don't believe it," and then does nothing about testing its disbelief I know that there will be doubt throughout this Conference I hope that there

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will be a minimum of skepticism and that when it arises it will shift to doubt and then to retesting.

One of Dr. Fremont-Smith's favorite topics is the reaction expressed in the statement, "I have repeated his experiments but I can't confirm his results." Dr Fremont-Smith insists that if you repeat experiments exactly, you will get an answer which will probably be the same answer that the other man obtained, though it may not be the entire answer. Repeating experiments exactly is made possible by conferences like this, in which the details of experiments may be inquired into and in which things omitted from formal papers can be brought out by direct questioning.

We are fortunate in having with us a number of visitors from abroad and also representatives from the Armed Forces We might begin by asking each of you to stand up, introduce yourself, and tell where you come from and what facet of this field you are particularly interested in.

STANLEY E. BRADLEY: I am interested in shock with particular reference to distal circulation.

JOHN M. HOWARD: I am a surgeon, and am here representing the Army's research program

E P. SHARPEY-SCHAFER: At St Thomas' Hospital, London, we are mainly interested in low blood pressure states in man.

ELLIOTT F. OSSERMAN: At the Naval Medical Research Institute, Bethesda, Md, we are primarily interested in thermal burns, frostbite, and immersion, and the shock states produced by these traumata

ALAN C. BURTON: I am from the University of Western Ontario I call myself a biophysicist, but that is just a kind of physiologist

MARGARET H SLOAN: I am from the National Research Council in Washington, D C I am representing Dr Winternitz, who wished me to express his great regret that he could not be here today

FRANCIS D. MOORE: I am from Harvard University and the Peter Bent Brigham Hospital Our interest has been in studying the metabolic response to trauma, shock, and burns as a clinical and chemical phenomenon

CHESTER HYMAN: I am from the University of Southern California We try our best not to limit ourselves to capillary permeability

MARK NICKERSON: I am at the University of Michigan Our primary interest for several years has been the role of the sympa-

thetic nervous system in regulating the circulation

R. E. HAIST: I am in the Department of Physiology, University of Toronto, Canada Our chief interest is in the metabolic aspects of shock

K. J. FRANKLIN: I am of St Bartholomew's Hospital Medical College, London, at present in the University of Illinois, Urbana, Ill, a physiologist interested in the normal circulation and in the departures from that normal which are manifested in shock

EUGENE STEAD: Duke University.

SHEILA HOWARTH: Institute of Cardiology, National Heart Hospital, London, England

GEORGE BURCH. Tulane University, New Orleans I have been particularly interested in the use of isotopes in studying electrolyte problems and congestive heart failure I have not done experimental work with shock

FRANK FREMONT-SMITH: I was trained in neurophysiology, then in psychiatry, and am now trying to find my way through the maze of administration

EPHRAIM SHORR· Cornell University Medical College and The New York Hospital, particularly interested in metabolic aspects of shock and their relation to circulatory homeostasis

THOMAS J HALEY· University of California at Los Angeles; I am interested in the shock phases of the radiation syndrome

HAROLD D. GREEN. Department of Physiology and Pharmacology of the Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N C I am interested in the measurement of blood flow and the factors that regulate blood flow.

BENJAMIN W. ZWEIFACH: Cornell University Medical College; primarily interested in what we call the terminal vascular bed and the capillary bed, and the factors which regulate the circulation

JACOB FINE: I am interested in the phenomenon of irreversibility in shock

RUSSELL NELSON: Walter Reed Army Medical Center in Washington, D C, before that from the University of Minnesota at Minneapolis, primarily interested in the problems of shock from bacterial invasion, and the metabolic derangements associated therewith

EWALD E. SELKURT. Western Reserve University, interested in peripheral circulation, with emphasis on the kidney

JOHN REMINGTON I am interested in all phases of the circulation

Shorr. Thank you. Since it was obviously impossible to arrange a conference to cover the whole field of shock, five topics were selected as being fairly comprehensive It has been found most useful, in these meetings, to start each topic with a discussion led by one member The presentation is not designed to be all-inclusive but rather to serve as a basis for the subsequent discussion. It is meant to be provocative, and it generally turns out that way

We have found it best to keep the introductory remarks to about one half-hour By the end of four or five minutes in most groups, questions are on the lips of everyone. Since we hesitate to interrupt a train of thought, which might not return, we have suggested that the initial speakers divide their presentations so that there are logical points at which they can be interrupted for a barrage of questions

The topic for this morning is, "Humoral Vasoactive and Other Metabolic Derangements in Shock" Dr Zweifach will open the session with a discussion of the concept of shock which has been advanced by my laboratory. It is based on the results of a study begun under Dr Robert Chambers at New York University, and, since 1945, extended and amplified at Cornell as a collaborative effort of Drs Zweifach, Mazur, Baez, Furchgott, and myself This concept, in brief, would relate a specific pattern of vascular events in the progression of the shock syndrome to the sequential development of specific metabolic alterations in kidney, liver, and muscle, which lead to the release of the vasoactive principles VEM and VDM My associates and I anticipate, and shall welcome, your critical assessment of this concept

Franklin Mr Chairman, would it be possible for you to define "shock" before we start?

Shorr I fear that if we began defining topics before we started, our first session might be dissipated I hope that a definition of "shock" which most of us can approve will emerge from the session

Franklin Could you tell us what you include in the scope of "circulation"? Are you including all the fluid movements within the body or merely that of the blood?

Shorr Yes, all the fluid movements

Franklin: Finally, would you like to define "homeostasis"?

Shorr It is used with the meaning Claude Bernard gave it all the factors that are involved in the maintenance of the constancy of the internal environment

HUMORAL VASOACTIVE AND OTHER METABOLIC DERANGEMENTS IN SHOCK*

BENJAMIN W ZWEIFACH
Department of Medicine, Cornell University Medical College

It is my purpose to present a particular point of view, with reference to the shock syndrome, which has been the outcome of experiments carried out during the past ten years (1,2,3). The experimental basis for this concept has been given in considerable detail in previous Macy Conferences (4,5). I do not think it is necessary to cover this data again. Rather, I should like to develop the experimental findings into a continuous sequence. I trust that the presentation will be sufficiently provocative to invite discussion of any part which is not clear

Functional alterations in various segments of the cardiovascular system have been intensively studied by numerous investigators in order to provide a clearer insight into the sequential changes which lead to the collapse of the peripheral circulation under different conditions These studies have included a wide diversity of measurements of different aspects of cardiovascular hemodynamics, many of which have only an indirect, and frequently highly involved, relationship to the basic feature of this problem, that of peripheral circulatory homeostasis The circulatory stress during shock is of sufficient magnitude to call into play all available homeostatic mechanisms Included in Table I are the most commonly accepted measurements of cardiovascular performance It is obvious that to this list could be added an almost endless number of parameters, each of which would show some change. The significance of changes in these parameters, with reference to specific derangements of the peripheral circulation, however, is not readily apparent. In final analysis, the principal function with which the circulation is concerned is the maintenance of tissue homeostasis in accord with local metabolic requirements The most critical aspects of this function are achieved by peripheral regulatory mechanisms

* This paper is based on studies conducted with Drs Abraham Mazur, Silvio Baez, Robert F Furchgott, and Ephraim Shorr, under grants from the Josiah Macy, Jr Foundation, Eli Lilly and Company, the National Institutes of Health, United States Public Health Service, and the Postley Fund

JOHN REMINGTON. I am interested in all phases of the circulation

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different tissues, with emphasis on the omental circulation (1) The highly complex regulation of the circulation through the terminal portion of the vascular tree was shown to be related to both humoral and neurogenic factors The participation of homeostatic mechanisms arising in the adrenals, the kidneys, and the sympathetic nervous system was demonstrated and characterized, as far as was possible, by using the various indices of peripheral functional activity listed at the bottom of Table I On the basis of this type of approach, it has been possible to recognize the contribution of specific mechanisms to the vascular readjustment following circulatory stress and to evaluate these in their proper perspective with regard to the sequence of changes leading to collapse and to the so-called irreversible stage of the syndrome. A concept of shock has been developed which is not all inclusive but serves to focus attention on vascular derangements in a critical area of the circulation (2,6,7)

The observations to be reported deal exclusively with hemorrhagic shock, unless otherwise stated Microscopic studies on the circulation in the mesentery or omentum of rats, cats, guinea pigs, and dogs have revealed an almost identical pattern of response in all these species Early in our studies, a survey was made of the circulation in tissues such as the skin, skeletal muscle, gut wall, intestinal mesentery, as well as the omentum The mesentery and omentum were selected for our studies on the circulatory changes during shock for several reasons Microscopic observations on the circulation in the skin showed an almost complete cessation of blood flow through this tissue following as little blood loss as 2 per cent of body weight Thereafter, throughout the subsequent progression of the hemorrhagic shock syndrome, the skin maintained a stagnant, ischemic type of circulation Preliminary studies were carried out on the circulation of the skeletal muscle, using the abdominal wall of the rat and the circulation in the distal portion of the tibialis anticus muscle of the cat In both of these capillary beds, the circulation was almost completely curtailed early in the syndrome and remained so throughout Furthermore, it was found that the surgical manipulation required to prepare such tissues for microscopic study seriously limited their value in terms of functional alterations within the terminal vascular bed

The omentum, on the other hand, could be readily exteriorized without interfering with the intrinsic behavior of the terminal vascular bed (8) Furthermore, the use of a nonparenchymatous tissue, such as the omentum, permitted observations on a circulatory bed which would be least affected by local changes within that tissue during shock and which could therefore serve as a guide

TABLE I

Hemodynamic Measurements in Hemorrhagic Shock

Criterion	Normal	Shock
Blood Pressure (mm Hg)	110	50
Heart Rate (beats/min.)	75	210
Cardiac Output (liters/min, Fick)	2 5	0.4
Right Auricular Pressure (mm saline)	35	10
Blood Volume (per cent of normal)	100%	65%
Blood Hematocrit (per cent cells)	45%	30%
Peripheral Resistance (dynes/sec /cm ^{2})	1200	1500
Peripheral Vasoconstriction	+	+++
Terminal Vascular Bed		
Vasomotion	Present	Augmented → Absent
Response to Epinephrine	+	+++ → ±
Capillary Blood Flow	Intermittent	Ischemic → Overall
Venular Return	Good	Slowed → Stagnant

Representative indices of cardiovascular function commonly employed in studies on shock None of the eight criteria listed (data compiled from literature) adequately reflect the sequence of changes in terminal vascular bed as given below The evolution of compensatory and decompensatory patterns of vascular response can be recognized in the terminal vascular bed

which are unique to the terminal vascular bed and which cannot be adequately reflected by hemodynamic measurements made solely on the larger vascular components

Our own approach to the problem has been to focus attention on the terminal vascular bed through direct microscopic observations on these vessels For this purpose we have selected criteria, based on many years of experience with normal control animals, which are descriptive of the functional status of the terminal vascular bed in terms of its capacity to operate as an independent functional unit Observations confined to the larger blood vessels have not been sufficiently revealing in this regard

An analysis of the factors which influence peripheral vascular behavior was made by direct visualization of the capillary bed in

bed in a structure such as skeletal muscle or skin. Finally, the responsiveness to given humoral principles, whether they be local in origin or blood-borne, will vary from tissue to tissue, depending upon the metabolic activity of that organ. Certain blood levels of epinephrine, for example, will produce vasoconstriction in the skin and either no constriction or a minimal one in the mesentery, and perhaps even a vasodilatation in skeletal muscle. All of these factors must be taken into consideration in evaluating, in proper perspective, the significance of what is being observed in the omentum during shock with reference to the behavior of the terminal vascular bed in other areas of the body. Organs such as the liver, kidney, and spleen, with a highly specialized vascular architecture, may show a sequence of changes which are different from those seen in tissues where the terminal vascular bed serves a purely nutritional function.

With this as a background, let us attempt to evaluate the significance of our omental observations with reference to the shock syndrome as a whole, and to the terminal vascular bed in particular organs. The omentum, as a visceral structure, should reflect the relative participation of neurogenic and humoral factors in other splanchnic organs. Further, with reference to the systemic blood pressure, it provides us with an index of the adequacy of the arterial perfusion of the terminal vascular bed. The larger blood vessels in the mesentery and in the omentum are under the influence of the sympathetic nervous system, and when this mechanism becomes activated during circulatory stress, the degree of vasoconstriction in the larger arteries and veins can be readily ascertained. The venous blood from the omentum and mesentery drains into veins which empty into the portal system. As a consequence, a portal hypertension, or interference with venous drainage resulting from changes in the liver proper, will be reflected by the ease with which blood drains from the omental venules into the larger venous radicals. This is especially useful in evaluating the response of the animal to transfusion. In irreversible hemorrhagic shock, an outstanding finding in the omentum is the failure to restore an effective return of blood in the largest veins which can be seen. This sluggish venous flow persists, despite the elevation of blood pressure to essentially normotensive levels, and precedes the ensuing progressive derangement of the terminal vascular bed. In experiments where various protective measures, such as sympathectomy or Dibenamine have been introduced, the venous outflow from the omentum into the portal system is remarkably well sustained even at blood pressures as low as 30 mm. Hg.

for the involvement of systemic factors. In addition, being a relatively nonparenchymatous structure, local factors of cellular metabolic origin, as a consequence of tissue hypoxia, will not complicate the response of the terminal vascular bed during stress The changes which develop within the omental circulation must therefore be attributed either to neurogenic factors or to humoral vasoactive principles introduced by way of the blood stream

Moore There have been some observations in the skin and some in the conjunctiva and some in the mesentery, but in all instances one is dealing with circulation to a metabolically inactive and unimportant area from the point of view of cell respiration. I should like to raise the question, perhaps for further discussion by you or by somebody else, as to whether or not in a vital visceral organ such as liver, kidney, or brain, where maintenance of cell respiration is more essential to survival, one might not find something different. This same sequence might take place on a different time schedule or an entirely different sequence might be seen

Zweifach. The relevance of circulatory observations in the omentum to the changes which develop in other tissues should be considered in the light of a number of considerations It is obvious that each organ has its own metabolic peculiarities which would be differently affected by a reduction in blood flow to the tissues, such as occurs in shock That the local factor, in terms of vascular homeostasis, is of considerable importance is attested to by the abundant evidence in the literature characterizing the type of reactive hyperemia which develops in different tissues following various degrees of circulatory arrest The local factor can only be evaluated by observations made directly on the particular structure A tissue, such as the omentum, can perhaps serve as a guide to the general tendency of the vascular reactions which develop following a given type of circulatory stress The effects of local metabolites are minimal in the omentum or mesentery

Although the same basic structural pattern exists in the terminal vascular bed of almost all tissues, it should be recognized that there are considerable variations, with respect to the number of true capillaries, the muscularity of the metarterioles and the precapillary sphincters, and the presence or absence of direct A-V shunts, all of which will influence the quantitative aspects of the response The extent of the sympathetic innervation of the terminal vascular bed varies in different organs The terminal vascular bed in the omentum represents an area in which the neurogenic control of the terminal vascular bed is minor when compared with the vascular

bed in a structure such as skeletal muscle or skin Finally, the responsiveness to given humoral principles, whether they be local in origin or blood-borne, will vary from tissue to tissue, depending upon the metabolic activity of that organ Certain blood levels of epinephrine, for example, will produce vasoconstriction in the skin and either no constriction or a minimal one in the mesentery, and perhaps even a vasodilatation in skeletal muscle All of these factors must be taken into consideration in evaluating, in proper perspective, the significance of what is being observed in the omentum during shock with reference to the behavior of the terminal vascular bed in other areas of the body. Organs such as the liver, kidney, and spleen, with a highly specialized vascular architecture, may show a sequence of changes which are different from those seen in tissues where the terminal vascular bed serves a purely nutritional function

With this as a background, let us attempt to evaluate the significance of our omental observations with reference to the shock syndrome as a whole, and to the terminal vascular bed in particular organs The omentum, as a visceral structure, should reflect the relative participation of neurogenic and humoral factors in other splanchnic organs Further, with reference to the systemic blood pressure, it provides us with an index of the adequacy of the arterial perfusion of the terminal vascular bed The larger blood vessels in the mesentery and in the omentum are under the influence of the sympathetic nervous system, and when this mechanism becomes activated during circulatory stress, the degree of vasoconstriction in the larger arteries and veins can be readily ascertained The venous blood from the omentum and mesentery drains into veins which empty into the portal system As a consequence, a portal hypertension, or interference with venous drainage resulting from changes in the liver proper, will be reflected by the ease with which blood drains from the omental venules into the larger venous radicals This is especially useful in evaluating the response of the animal to transfusion In irreversible hemorrhagic shock, an outstanding finding in the omentum is the failure to restore an effective return of blood in the largest veins which can be seen This sluggish venous flow persists, despite the elevation of blood pressure to essentially normotensive levels, and precedes the ensuing progressive derangement of the terminal vascular bed In experiments where various protective measures, such as sympathectomy or Dibenamine have been introduced, the venous outflow from the omentum into the portal system is remarkably well sustained even at blood pressures as low as 30 mm Hg

With respect to the participation of humoral factors, the omental circulation provides us with an extremely delicate tool for the detection of such blood-borne agents The possibility exists that the extent to which these agents will affect the vascular response in other tissues may be neither the same as, nor directly comparable with, the omental response. However, observations carried out on over five hundred dogs subjected to shock reveal an amazingly close parallel between the decompensatory tendency in the omentum and a similar tendency in other visceral structures, such as the gut and liver. In every instance where an animal is sacrificed or dies during the compensatory stage of shock, the gut circulation is likewise ischemic and restricted, and the mucosal surface shows no evidence of congestion The liver is pale and, on section, very little blood oozes from the cut surface In contrast, when an animal is sacrificed in the decompensatory stage of shock, either before or after unsuccessful blood replacement, the gut is congested and hyperemic, the mucosal surface is dusky, and the liver is dark and feels tense, upon section, blood oozes from the incision. We therefore feel that the omental observations provide positive information with respect to the vascular tendencies in other visceral structures Certainly, the direct correlation between decompensatory changes in the omentum and the irreversibility of the syndrome supports this contention Thus far, there is no evidence to indicate that the changes observed in the omentum are peculiar to that organ and that other splanchnic tissues show a different pattern of response

Shorr Dr Moore, I should like to return to the statement you made Isn't it an unusual assumption that the organs in the abdomen are nonessential?

Moore That would be a terrible assumption I meant that the mesenteric fat to which these vessels supply blood, if I understand it rightly, is very unimportant as opposed, let's say, to the liver or the kidney, which I think we will agree, are both quite essential intra-abdominal organs

Fremont-Smith To justify Dr Moore's first comment, when one thinks of the central nerves or the respiratory centers, it is perfectly obvious that this series of changes cannot take place there Therefore, there is no question that vascular beds in different parts of the body will react differently to the conditions of shock which are being described

And, if I may paraphrase him, what Dr Moore is saying simply is since we know that is so in the central nervous system, it may very well be true in other parts of the body not studied by this

technique Dr Zweifach says it certainly may So there is no disagreement

Moore: I am not disagreeing at all I am just trying to point up the fact that we are looking at the circulation in some fat, and that the circulation in the coronary area, in the liver, in the renal cortex, and possibly in the adrenal cortex just might be following other procedures

Zweifach It is obvious that no claims are being made that the vascular changes in the omentum per se represent the critical defect bringing about a deterioration of the shock syndrome It should be emphasized that observations confined to any other organ would be equally limited, perhaps even more so, to that particular structure

Moore Of course, and I understand that you are describing what you can study so beautifully and what, because of its availability for observation and study, has yielded so much important information

Fine. I think it is important to consider the possibility that this may be a special case While I believe it does not reflect a fundamental difference between this tissue and other tissues, there is this to consider that in irreversible shock there is intestinal hemorrhage, and that intestinal hemorrhage is a rather special feature of shock Little or no hemorrhage is seen in other tissues If you produce a by-pass by making an Eck fistula, this hemorrhage is avoided

Zweifach I do not believe that the data presented have indicated that vascular decompensation is not occurring within the intestinal tract On the contrary, the omental data suggest that the gut and liver are the two major organs in which vascular decompensation is occurring Our previous studies, buttressed by more recent data, have stressed the obvious vascular decompensation in the liver, both as a site for the sequestration of blood from the active circulation and as a factor leading to stagnant hypoxia within that organ Dr Fine's recent work with antibiotics has brought into focus the importance of the gut factor with reference to bacterial infection during the irreversible tendency of the shock syndrome Whether the gut factor is primary to the subsequent derangement of the liver circulation, or vice versa, or whether a combination of the two factors is responsible for irreversibility remains the subject for future investigation

ANATOMY OF OMENTAL VASCULAR BED

From a functional consideration, there are two major subdivisions of the peripheral vascular system (9) The first includes the large arteries and veins which serve as conduits bringing blood to and

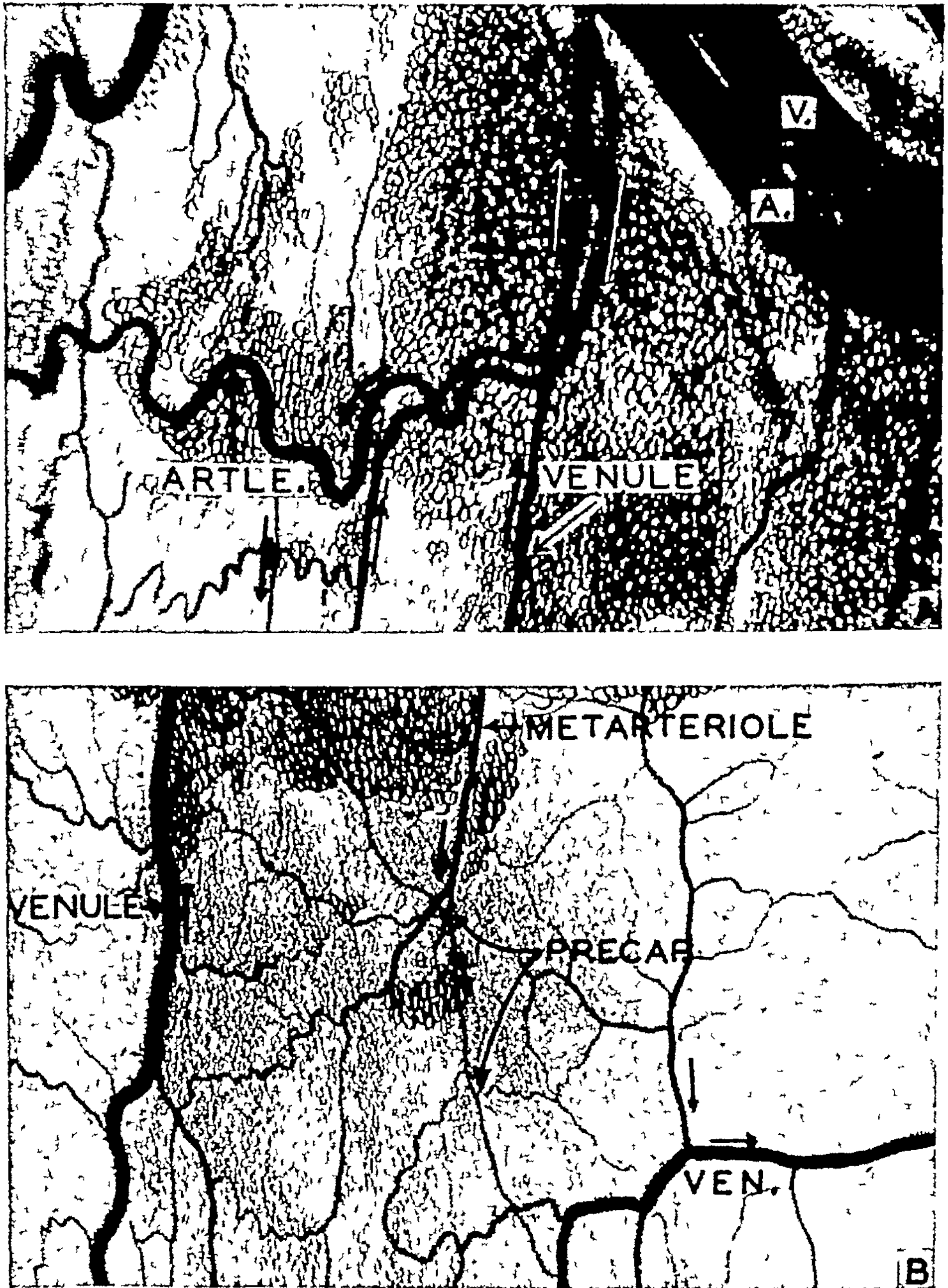


FIGURE 1 Two photomicrographs of peripheral blood vessels in mesentery of normal rat (40x) A Ultimate subdivisions of larger blood vessels Small artery (A) and vein (V) in upper right corner Arteriolar branch (artle) and accompanying collecting venule (venule are vessels directly contiguous with capillary bed B Terminal vascular or capillary bed Functional unit organized about centrally located metarteriole and its side branches Junctional segment of offshoot is muscular and referred to as precapillary sphincter (precap) Precapillaries subdivide to form network of true capillaries, which are purely endothelial and nonmuscular Direct continuations of metarterioles join to form nonmuscular venules (ven) which drain into muscular collecting venules (venule) Arrows indicate direction of blood flow

from the tissues Following repeated subdivision, the small arteries branch into the arterioles, which then enter the tissue proper Up to this point, the principal function of the vascular tree has been to maintain the blood in a forward motion under a sufficiently high pressure to perfuse the tissues Figure 1A, a photomicrograph of the circulation in the mesentery of the dog, illustrates the branching of the larger blood vessels into the ultimate subdivisions of the vascular tree The arterioles and accompanying venules are present as paired vessels just proximal to the capillary bed The arterioles in this figure are approximately 100 micra in diameter Changes in caliber of these vessels are of paramount importance in maintaining the blood pressure Distal to this point, the arterioles subdivide to form the group of vessels collectively referred to as the "capillary bed" Included in this functional unit are the metarterioles, precapillaries, capillaries, and collecting venules Although these vessels are structurally different, they are organized in a discrete pattern, admirably suited for their functioning as a collective unit Figure 1B is a photomicrograph of the capillary bed in the mesentery The structural make-up of the capillary bed is organized about centrally placed preferential channels, the metarterioles, which are the direct continuation of the arterioles The capillary vessels can be seen to be formed by side offshoots of the metarterioles The junctional segment of these offshoots is referred to as the precapillary sphincter and is surrounded by smooth muscle only in this proximal zone Beyond this point, the vessels, which subdivide to form a network of capillaries, are purely endothelial tubes with no muscle cells in their walls These, therefore, are the true capillaries The collecting venules within the capillary bed are likewise nonmuscular I should like to call your attention to the presence of direct interconnections between arterioles and venules in the microscopic field which is shown in Figure 1B Such interconnections between arterioles and venules have been seen in the mesentery, in the wall of the gut, in the skin, and in skeletal muscle

Bradley Do you intend to generalize from this to all capillary beds?

Zweifach It is difficult to make any generalization other than that these anastomoses are present in a wide variety of vascular beds

Franklin Are those true arteriovenous anastomoses of the typical structure?

Zweifach I would say that there are two categories of direct shunts between arterioles and venules One is of a type directly comparable to the Suquet-Hoyer canals, which have been described

in the skin between large arteries and veins In the smaller blood vessels, these interconnections are surrounded by muscle only along the proximal half of the shunts and are purely endothelial in the remaining portion The factors which regulate the activity of these shunts are poorly understood However, there are situations in which the blood flow can effectively by-pass the entire capillary bed through these interconnections The shunts in the wall of the gut are especially active. In the open state, the blood is shunted away from the outer serosal surface toward the mucosa of the gut wall

INDICES OF VASCULAR BEHAVIOR

Included at the bottom of Table I (p 16) are four indices of peripheral vascular behavior which were found to undergo characteristic alterations during the shock syndrome The term "vasomotion" refers to periodic alterations in caliber of the muscular vessels in the capillary bed which vary in rate, intensity, and relative duration of the constrictor and dilator phases The term "augmented" refers to an increase in the rate, as well as in the duration, of the constrictor phase Active changes in blood flow through the capillary bed are brought about by selective constriction of these metarterioles and precapillary sphincters The true capillaries do not exhibit active changes in caliber Under normal circumstances, the blood flow through the capillary bed is intermittent, being for the most part restricted to the preferential channels and spilling over into the network of true capillaries only for relatively short periods This spontaneous periodicity appears to bear no relationship to vasomotor patterns in the large blood vessels

The vasoconstrictor response of the metarterioles or precapillaries to epinephrine applied topically serve as an additional parameter of "vascular reactivity"

Moore Have you used the classic pharmacologic preparation of so-called epinephrine, or have you limited yourself to norepinephrine in studying the peripheral circulation?

Zweifach Changes in the responsiveness of these vessels to epinephrine serve as a relative measure of their functional capacity to respond to a physiologic stimulus Identical changes in reactivity have been obtained when norepinephrine was used as the stimulating agent Assay curves obtained on the same sample, with both epinephrine and norepinephrine, are almost indistinguishable The development of hyperreactivity to exogenous epinephrine applied topically does not necessarily imply that this represents the physiologic adaptation which develops in the body On the other

hand, the observations do not preclude such a relationship The hypersensitivity to epinephrine may indicate an enhanced reactivity to other pressor systems, such as sympathin Furthermore, no direct inferences can be drawn concerning the effect of intravenously administered epinephrine on the vascular system during these periods We have not found it possible to correlate directly the hyperreactivity demonstrated by the local application of pressor drugs with a corresponding systemic hyperreactivity to these drugs

Capillary blood flow is evaluated in terms of whether it is intermittent or continuous, ischemic or over-all, and the extent to which it remains confined to certain preferential channels The adequacy of the outflow of blood from the capillary bed into the collecting venules serves as a good index of the relative efficiency of peripheral vascular mechanisms in actively aiding the *vis a tergo* of the arterial circulation.

The term "vasoconstriction" has been reserved for those changes in the terminal vascular bed which occur rapidly in response to vasoactive drugs or to neurogenic stimuli Such changes are seen only in the metarterioles, the precapillary sphincters, and to a lesser degree in the muscular venules Vasoconstriction in Table I (p 16) and Figure 2 (p 28) refers to the terminal arterioles which are just proximal to the capillary bed proper

Vasoconstriction of the larger blood vessels, for the most part, is mediated by way of adaptive reflexes, which originate in receptors in the major blood vessels (10) and appear to bear no direct relationship to the blood flow in the terminal vascular bed These reflexes operate, of course, by way of the sympathetic nervous system When the sympathetic nervous system is directly stimulated, or the vasomotor center is acutely discharged by a suitable stress situation, a rapid and intense vasoconstriction of the entire arterial tree within the mesentery can be observed, down to and including the terminal arterioles Distal to this point, in the capillary bed proper, there is no active vasoconstriction under these circumstances The terminal vascular bed undergoes its own type of compensatory readjustment, dependent, as we have shown, for the most part upon humoral factors There is no sharp line of demarcation between what we refer to as the large blood vessels and the terminal vascular bed Actually, the terminal arterioles, of the type seen in the photomicrograph of Figure 1, represent an intermediate segment between the large blood vessels on the one hand and the terminal vascular bed on the other As such, they are under the influence of mechanisms which affect both segments of

the vascular tree For example, the terminal arterioles are the vessels which undergo reflex dilatation in experiments with local microtrauma. These vessels, together with the terminal vascular bed, are the vascular units which are directly influenced by local metabolic changes within the tissue It is difficult to conceive of a metabolic mechanism of local tissue origin which would affect the larger blood vessels, unless the mass of tissue was sufficiently large to introduce these metabolites into the systemic circulation.

Nickerson To what point are you going back when you speak of constriction?

Zweifach As previously indicated, the vasoconstriction in the largest blood vessels which are microscopically visible is not uniform in different tissues This perhaps may be related to differences in their innervation rather than to metabolic peculiarities of the tissues which they perfuse with blood

Nickerson Is this vasoconstriction equally marked in shock precipitated by factors other than hemorrhage?

Zweifach· Profound vasoconstriction develops in experiments where there is a considerable reduction in blood volume In traumatic shock, vasoconstriction is not as prominent as in hemorrhage In shock produced in dogs with arterial tourniquets on both hind limbs for ten to twelve hours, the application of plaster casts, just prior to the release of the tourniquets, reduces the local swelling of the damaged limbs but does not prevent the development of fatal shock In such animals, vasoconstriction is minimal A great many ancillary factors contribute to the breakdown of the circulation under different circumstances The compensatory and decompensatory response is a composite of changes in the heart, the arteries, the veins, and the terminal vascular bed. The compensatory adjustment of each segment will vary widely A deficiency in the response of one segment is usually counterbalanced by overcompensation in the other segments in an effort to achieve homeostasis

Nelson Would you explain the difference in your denotation of the words "reactivity" and "vasomotion," and how they differ from vasoconstriction?

Zweifach The term "reactivity" refers to the responsiveness of the muscular components of the terminal vascular bed to a locally applied stimulus, such as epinephrine The response to epinephrine is then used as a measure of the functional status of the vascular neuromuscular effector units Hyperreactivity and hyporeactivity, as used in this presentation, refer only to the constrictor response to topical epinephrine We have not made an intensive study of the reactivity of these vessels to other pressor or depressor agents dur-

ing the two phases of shock. The specific vessels which are observed are the metarterioles and the precapillary sphincters Under normal conditions they represent the components of the terminal vascular bed which are most highly responsive to humoral agents The larger blood vessels, such as arterioles and muscular venules, respond only to the topical application of higher concentrations of epinephrine Their behavior is not included in the present considerations on vascular reactivity

The term "vasomotion" also refers to a phenomenon unique to the terminal vascular bed Under normal conditions, the blood flow through the capillary bed is sporadic and intermittent The circulation becomes periodically restricted to certain preferential channels (see Figure 1B) This is followed by a brief period in which the precapillary sphincters dilate, bringing about an active perfusion of blood through most of the capillary vessels These periodic excursions in caliber of the metarterioles and precapillaries develop spontaneously over a period of several minutes Under certain experimental conditions, the cyclic variations may become as frequent as once every fifteen to twenty seconds The relative duration of the two phases (i e, whether there is a long vasoconstrictor phase and a short vasodilator phase, or vice versa, a long vasodilator phase and a short vasoconstrictor phase), has a profound influence on the direction and extent of fluid exchange within the capillary bed. Peripheral vasomotion has been found to change independently of comparable vasomotor excursions in the larger blood vessels

Fremont-Smith· It is a response of vasomotion?

Zweifach Although alterations in vasomotion and reactivity to epinephrine usually develop in the same direction following stress, disturbances in one mechanism can develop independently of the other

RELATIONSHIP OF ADRENAL, KIDNEY, AND SYMPATHETIC NERVES TO VASCULAR REACTIVITY

Moore As you define your criteria, the adrenal medullary has nothing to do with vasoconstriction and vasomotion

Zweifach There is no experimental evidence directly relating the adrenal medullary secretions to vasomotion In experiments where epinephrine is injected intravenously, in a dose sufficient to produce a transient rise in blood pressure of about 30 to 40 mm Hg, no effect on vasomotion is seen The reactivity of the precapillaries to topical epinephrine shows only a fleeting increase In Figure 2 which lists the factors affecting peripheral vascular behavior, the adrenal medulla is not included as a factor influencing the vasoconstriction following stress This does not imply that the intra-

venous injection of epinephrine does not produce a vasoconstriction of the peripheral blood vessels. It merely indicates that, in the absence of the adrenal medulla, the capacity of the blood vessels to undergo active vasoconstriction does not become impaired following a standardized stress, such as acute hemorrhage

	Intrinsic Tone	Reactivity	Vasomotion	Vasoconstriction
Sympathetic Nervous System		*	*	*
Adrenal Cortex	*	*	*	*
Adrenal Medulla		*		
Renal		*		*
Hepatic		*		
Local Tissue Metabolism	*	*		

FIGURE 2 The regulation of blood flow through the terminal vascular bed is a composite of multiple interlocking controls Listed above are four functional indices which were routinely studied in the response to circulatory stress *Intrinsic Tone* of both the metarterioles and capillary endothelium, *Reactivity* of metarterioles and precapillaries to topical epinephrine, *Vasomotion* of metarterioles and precapillaries, *Vasoconstriction* of terminal arterioles The asterisk indicates a positive contribution by a particular homeostatic system

An analysis of the compensatory readjustments of the peripheral circulation following hemorrhage* indicates that the adaptive response is a composite of several factors For example, the reactivity of the muscular vessels in the terminal vascular bed to topically applied epinephrine becomes considerably potentiated during the initial compensatory phase of the syndrome Experimental removal of the kidney from the circulation blunts the hyperreactive response, as seen in Figure 3 In addition to the renal factor, the adrenal and sympathetic nervous systems both contribute to the compensatory response of the peripheral vascular bed Thus, in the sympathectomized animal the hyperreactivity to epinephrine is not as pronounced following bleeding When, in addition, the kidney is removed from the circulation, the hyperreactive response is further blunted Similar experiments on adrenalectomized, salt-maintained rats show a considerable blunting of the hyperreactive response following blood loss Renal ablation in adrenalectomized

* Zweifach, B W, Baez, S, and Shorr, E Unpublished data

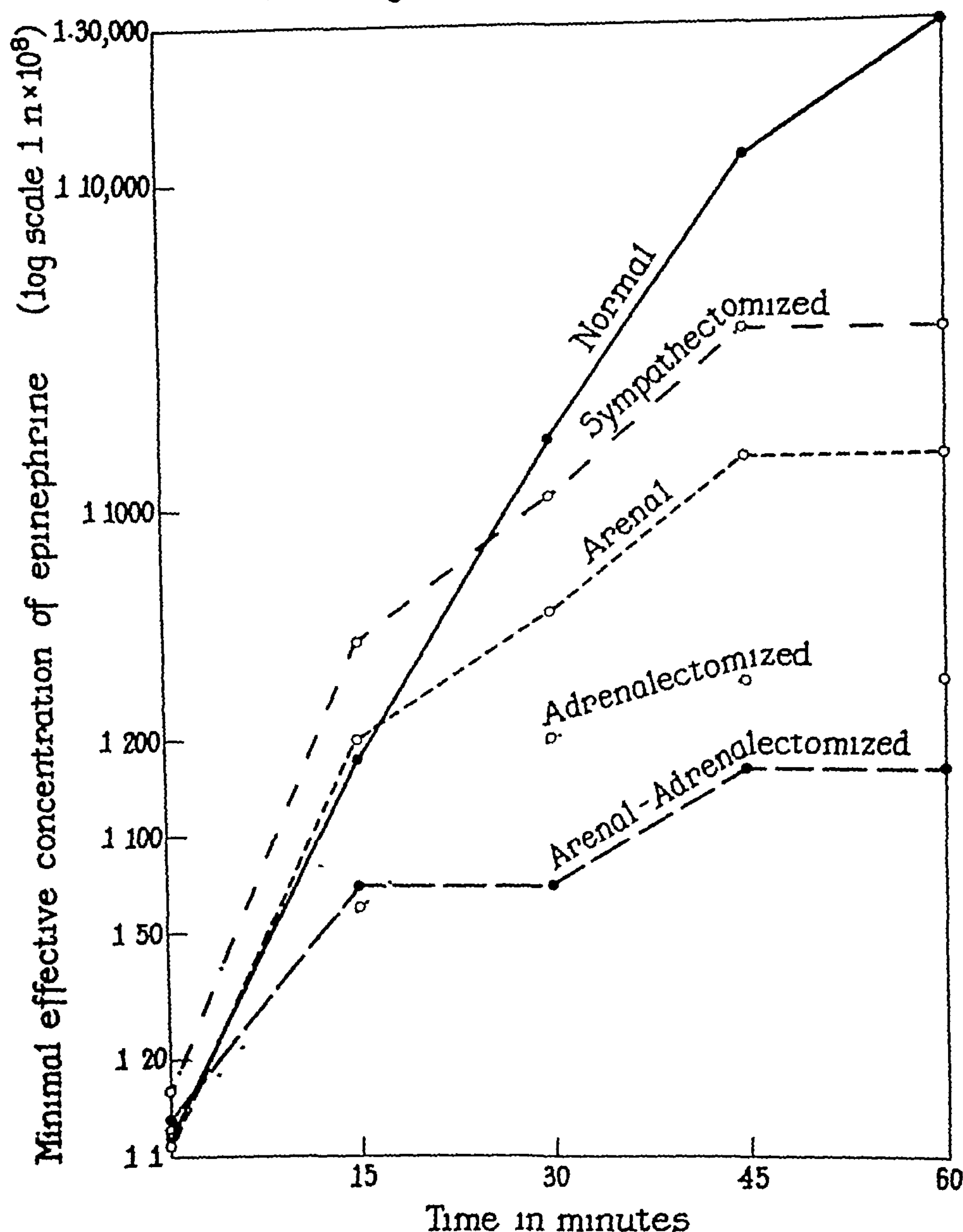


FIGURE 3 Development of vascular hyperreactivity to topical epinephrine as influenced by surgical ablation of different homeostatic mechanisms Vascular hyperreactivity progressively increases in normal controls until a maximum is reached about 60 to 90 minutes after bleeding Removal of kidneys or adrenals, or thoracolumbar sympathectomy, blunts both the degree to which the vascular response to epinephrine is potentiated and the rate at which this reaction develops

animals almost completely suppresses the hyperreactive response to hemorrhage The compensatory phase of peripheral vascular behavior was shown to be a composite of the activity of renal,

adrenal, and neurogenic homeostatic mechanisms superimposed on the intrinsic tone of the blood vessels themselves.*

Green: To topically applied epinephrine?

Zweifach: The data shown in Figure 3 are based on the responsiveness of the peripheral blood vessels in the mesentery as measured by the reaction to topically applied epinephrine.

Nickerson: Is this sympathectomy acute or chronic?

Zweifach: These studies in both the rat and the dog included animals which were subjected to bilateral thoracolumbar sympathectomy from two weeks to four months before the experiment.

Nickerson: Would you like to speculate on the relation between this blunting of the responsiveness to topically applied epinephrine and the classical sensitization by denervation?

Zweifach: Sympathectomy, by itself, increases the basal level of reactivity to epinephrine in the capillary bed. Thus, normal animals show a threshold response to the application of 1:2 million to 1:6 million of epinephrine. Following sympathectomy, the basal reactivity lies between 1:10 million to 1:40 million of epinephrine. The data presented refer to an increase in reactivity to epinephrine which develops following a given stress, such as hemorrhage. In the case of the sympathectomized animal, the maximal reactivity to epinephrine which develops is about 200 times that observed during the control period, whereas the maximal reactivity to epinephrine which develops in the normal animal is about 8500 times that of the control value.

Nickerson: This blunting, then, has nothing to do with what sympathectomy does to the sensitivity to epinephrine, but deals simply with what sympathectomy does to the effect of VEM on sensitivity?

Zweifach: As stated previously, the hyperreactivity which develops during circulatory stress reflects the contribution of several factors. The percentage of the increased reactivity in normal control animals which is due to VEM per se cannot be readily demonstrated.

Moore: This is VEM in the capillary bed that is circulating in the test rat? You have not added anything to your experimental animal except to test epinephrine?

Zweifach: I should like to emphasize that we are using the vasoconstrictor response to epinephrine as a means of measuring the functional status of the vessels in the capillary bed. The extent to which hyperreactivity develops is dependent upon the participation of different homeostatic mechanisms in the animal. Following

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* Zweifach, B. W., Metz, D. B., Baez, S. and Shorr, E. Unpublished data.

sympathectomy, a hyperreactive response to stress continues to develop. In terms of multiples of the basal response during the control period, the sympathectomized animal does not achieve a degree of hyperreactivity equivalent to that of normal animals subjected to identical hemorrhage.

Burton: But the animal is more reactive to epinephrine anyway after it is sympathectomized. So what is meant by saying that it develops less excess reactivity after bleeding?

Zweifach: The precise significance of the increased vascular reactivity following sympathectomy is difficult to interpret. The terminal arterioles of both normal and sympathectomized animals maintain an identical tonic vasoconstriction in the control state, despite the fact that their reactivity to epinephrine differs considerably. In other words, the degree of vasoconstriction or dilatation which these vessels show under different conditions is not necessarily reflected by their responsiveness to epinephrine. Furthermore, in considering the change in reactivity which develops following stress, we are faced with the difficulty of ascertaining whether a change in reactivity from 1:2 million of epinephrine to 1:40 million is equivalent to a change in reactivity from 1:20 million to 1:400 million. Both represent a twentyfold change from the initial basal response. It has been our practice to represent the changes in reactivity in terms of multiples of the original threshold response rather than in actual units of epinephrine.

Nickerson: Do you feel that this effect of sympathectomy is mediated directly upon these terminal precapillary sphincters, or could a good part of it be due to a change farther back in the vascular bed, so that the head of pressure which is presented to the precapillary sphincters is greater in the sympathectomized animal because he does not have the arteriolar and small arteriole vasoconstriction?

Zweifach: Our present evidence indicates that sympathetic nerve fibers directly supply the peripheral blood vessels up to and including the terminal arterioles, together with a variable portion of metarterioles (9). Beyond this point, many of the precapillary sphincters, and the distal continuations of the metarterioles, show no anatomical continuity with the sympathetic nervous system. Nevertheless, sympathectomy affects the reactivity of all the metarterioles and precapillaries. We assume that chemical mediators, liberated by the sympathetic nervous system at its nerve endings in the arterioles, are carried distally by the blood stream and thereby affect the reactivity of muscular structures beyond the point where

adrenal, and neurogenic homeostatic mechanisms superimposed on the intrinsic tone of the blood vessels themselves *

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a consideration of locally elaborated tissue metabolites was to draw attention to the possibility that in certain organs the local effects of hypoxia, etc., might influence the response of the terminal vascular bed during circulatory stress.

Nickerson. The lack of change in the degree of vasoconstriction might simply mean that the local tissue damage is in too small a part of the total area supplied by an arteriole. It is not really a test of the effect of tissue metabolism on the arterioles.

Zweifach. In an experimental study of the effects produced by purely local factors on the vascular system, the following technique was employed. It was possible, by using the manipulation technique, to introduce highly localized microtrauma with microneedles, or to inject, with a micropipette, specific irritants or metabolites. When controlled in this fashion, the effects produced by these procedures on the vascular system remain localized to that specific area. When a more extensive tissue mass was involved, in addition to the local effect, a dilatation of the arterioles just proximal to the capillary bed was seen. We have interpreted this to represent a local reflex arc since the effects could not conceivably be attributed to a diffusion of substances from the affected area to the dilated arterioles. It would be difficult to determine whether, in a tissue such as skeletal muscle, the local accumulation of some metabolites might not have a direct effect on the larger blood vessels.

Vessels of the caliber of several hundred micra and less, which have no well-defined connective tissue coats and are imbedded in the tissue, are probably directly influenced by the diffusion of metabolites into the extracellular fluids. A good example of this can be seen in observations made on the blood flow in skeletal muscle following hemorrhage. Normally, with the acute removal of 2 to 3 per cent of body weight of blood, the terminal arterioles undergo profound vasoconstriction and the capillary bed becomes highly ischemic in the skeletal muscle of the abdominal wall. If, prior to bleeding, one set of muscles is caused to contract by repeated electrical stimulation of a motor nerve for a period of several minutes, blood loss will then produce an extensive vasoconstriction in the opposite muscle which was not metabolically active, but will no longer produce a comparable vasoconstriction in the muscle which has been electrically stimulated. The terminal vascular bed in this area remains dilated. Although the arterioles are dilated, the capillary blood flow becomes stagnant as a consequence of the fall in blood pressure and of the vasoconstriction of large blood vessels outside the muscle proper.

sympathetic fibers can be demonstrated. Acute denervation brings about an increased blood flow through the terminal vascular bed as a consequence of the dilatation of feeding arterioles. However, after several days these vessels resume their original tonic state, so that the appearance of the capillary circulation in the sympathectomized animal is indistinguishable from that in normal controls. I have interpreted the increased reactivity of the sympathectomized bed to represent the greater participation of humoral factors in vascular control. It is apparent that unless some readjustment is made in the terminal vascular bed following sympathectomy, the precise equilibrium which maintains tissue homeostasis would be considerably altered.

INFLUENCE OF LOCAL TISSUE METABOLISM ON VASCULAR REACTIVITY

Nickerson. Before you go on, could you expand on the evidence from which you conclude that local tissue metabolism does not affect the vasoconstriction?

Zweifach. The term "local tissue metabolism" is used with reference to changes in vascular behavior which are introduced by purely local phenomena within the tissue proper. Unfortunately, we do not have sufficient evidence to be more specific, either in terms of pH, lactic acid, adenosine derivatives, or other by-products of tissue metabolism. Local factors play an important role in increasing the capillary blood flow in accord with changes in the metabolic activity of the tissue. For example, in skeletal muscle following muscle work, or in the mesentery following mild local trauma, the localized vasodilatation which develops is accompanied by a refractoriness of the muscular vessels, especially the precapillaries (11). No change in vasomotion was evident unless the trauma was severe enough to produce capillary stasis. The degree of vasoconstriction of the terminal arterioles leading into the capillary bed was not affected by purely local changes in tissue metabolism.

Nickerson. By vasoconstriction you are referring to the caliber of arterioles?

Zweifach. Yes, the terminal arterioles.

Nickerson. And you feel that this caliber is not altered by the level of tissue metabolic activity?

Zweifach. Not unless an extensive mass of tissue is traumatized.

Nickerson. That would be at variance with our interpretation.

Zweifach. The factors listed in Figure 2 relate specifically to the terminal vascular bed. I did not intend to include any of the larger blood vessels to which you are referring. My purpose in interjecting

lumen However, after a period of about twenty to thirty minutes, there develops a progressive narrowing of these capillaries which is most pronounced in the central segments of the vessels and gradually spreads in both directions along the length of the capillary

Fremont-Smith In other words, when the pressure is lowered in a capillary, the capillary diameter becomes narrower?

Zweifach With time

Fremont-Smith Are you saying that it is the elasticity of the capillary wall which causes it to contract, since there is no muscle involved?

Zweifach Yes

Remington Do those endothelial cells swell or shrink?

Zweifach The endothelial cells tend to thicken and bulge into the lumen

Remington Is there a shortening in the length?

Zweifach Narrowing of the true capillaries is accompanied by a longitudinal folding of the surface and bulging inward of the endothelial nucleus Frequently, the nucleus protrudes into the lumen sufficiently to impede the passage of blood beyond that point Several workers (13) have ascribed this endothelial narrowing to an active swelling of the endothelial cell

Stead Does any of the blood leak out and make the lumen smaller?

Zweifach The perviousness of the capillary wall does not seem to be increased in the narrowed state There is no extravasation of blood cells In other words, the change in shape of the endothelial cells during this process does not involve the separation of contiguous cell borders to produce stoma

Moore Under what conditions does such capillary narrowing occur?

Zweifach The above observations refer to the normal circulation in the mesentery or omentum of the rat, cat, or dog under the influence of a variety of anesthetic agents Excessive handling of the preparation, stretching the tissue, or inadequate control of the temperature of the exposed structure will completely abolish this type of endothelial narrowing

Burch If you obstructed both ends of a true capillary after it is devoid of blood, would the lumen change size by gathering fluid from the intercellular spaces?

Zweifach In experiments where both the entrance and exit of a capillary vessel were obstructed by microneedles, no change in the caliber of the vessel developed over a period of time comparable

Nickerson. The concept has arisen from different types of experiments that the effect of local tissue metabolic activity is one of the major factors in regulating the degree of vasoconstriction in a wide variety of organs

CAPILLARY TONE

Zweifach The extent to which the true capillaries can actively control the blood flow through them has been a controversial point. Under many conditions the true capillaries narrow when they are devoid of an active blood flow for protracted periods of time This type of capillary narrowing develops in the following manner: contraction of the precapillary sphincters interrupts the perfusion of arterial blood through the capillary. Despite this, the blood continues to be drained out of the capillaries into adjacent venules, which have an active circulation, or into the distal continuation of the preferential channel The capillary then remains empty of blood cells and, unless seen in a transparent structure such as the omentum, could be inaccurately interpreted as having undergone contraction The vessel then undergoes gradual narrowing as described above With the readmission of blood, as a consequence of precapillary dilatation, the narrowed capillary immediately resumes its original caliber I have preferred to ascribe such changes in diameter to the intrinsic tone of the capillary wall rather than to include them under the term "contractility" (12)

Bradley What do you mean by the "intrinsic tone of the endothelium"?

Zweifach The term "tone" with respect to the capillary wall has been used to describe an inherent elasticity which that structure possesses under normal conditions This property prevents the vessel from undergoing excessive dilatation and enables it to maintain a relatively constant diameter despite excessive increases in intravascular pressure Capillary tone resides in the endothelial cells themselves and, as in other cells, enables them to maintain a certain shape in relation to their environment Some investigators believe this to be a property determined by the selective exchange of electrolytes and water across the cell membrane

It is possible for capillary tone not only to be varied, but to be lost under abnormal or pathological conditions During periods of relative ischemia, in which the blood flow is confined to the preferential channels, the true capillaries have no active circulation of blood for periods of from several minutes to frequently as long as thirty to forty minutes These "inactive capillaries" show no change in caliber, despite the complete absence of any blood cells within their

over the literature from time to time, hoping to find objective information on this point, but it seems to me that many of the requisite data are lacking To say that these things actually change their elastic properties would require simultaneous direct measurements of intraluminal pressure and capillary diameter, which would make possible calculation of elastic coefficients at various times

Do you feel that the evidence available today permits us to say that the capillary wall actually can show a change in its elastic characteristics?

Zweifach Evidence for a variable tone in the capillary wall can be seen in the following observations first, in the intact circulation through the mesentery of the rat or frog, rubbing of the tissue adjacent to the capillary wall with a microneedle will produce a localized distension of the vessel in that particular area So far as could be ascertained, there was no change in the amount of blood which was being perfused through that particular capillary. Secondly, experiments were carried out in which the mesentery was perfused, in an otherwise intact animal, through a major arterial branch of the tissue In this type of experiment, the perfusion pressure can be changed over a rather wide range, from 20 to 150 mm. Hg, without producing any visible distension of the capillaries However, if one irritates a local segment of the capillary bed with a microneedle and then repeats the experiment, capillary dilatation develops in the manipulated capillaries with a pressure increment as small as 30 to 40 mm Hg

Hyman The same results could be explained if the stopcocks before the vessels you looked at opened up a bit as a result of the trauma, changing the effective perfusion pressure in the area studied

Fremont-Smith In other words, there was actually no pressure change in the first instance?

Hyman A lesser change in the capillary bed than in the second case

Zweifach I do not believe that conclusions with reference to capillary tone can be drawn from perfusion experiments on isolated limbs We found that the perfusion of excised organs does not bring about a uniform circulation through all of the available capillary channels (14) In fact, in instances where a completely cell-free or nonparticulate perfusion medium is used, only a small fraction of the capillary bed contains an active circulation The aforementioned data were obtained in perfusion experiments on tissues which were simultaneously observed under the microscope

to that noted above However, it must be remembered that mechanical handling of the tissues, even on a microscale, is frequently sufficient to interfere with the normal pattern of response Narrowing of the capillary vessels occurs only in the absence of an active circulation through them. I have never observed capillary narrowing during periods in which the vessel contained an active flow of blood On the other hand, a widening of the capillary from its previously narrowed state occurs only when an active flow of blood is reintroduced into the capillary It does not occur in the absence of an active circulation

Green Would it be possible to put a capillary pipette into one of these normal capillaries and still have it remain normal as the pressure changes?

Zweifach An experimental procedure, such as the introduction of a micropipette into a capillary, creates a highly abnormal situation I do not think valid conclusions can be drawn from such experiments with reference to normal capillary tone

Hyman How do you know the tone?

Zweifach The term "tone" is merely used to describe the normal state of the endothelial wall Under conditions of local inflammation or tissue trauma, the vessels appear to have suffered a loss of tone I have no observations which would indicate that it is possible for a capillary to have hypernormal tone Obviously, there must be gradations between these extremes Unfortunately, there are no methods available which permit quantitation of such gradations

Fine Even though you speak of tone of the capillary wall, functionally the capillary is nevertheless a passive tube, is it not?

Zweifach I believe that changes in caliber of the capillary vessels are secondary to changes in the blood flow through them but are also conditioned by the degree of cell tone in the endothelium.

Hyman Is the capillary the equivalent of a rubber balloon with a constant elasticity, or do you imply that it has a variable elasticity?

Zweifach The endothelial wall will differ from an inert substance, such as rubber, which possesses a fixed type of elasticity Endothelial tone, or elasticity if you prefer to use that term, is a variable function dependent upon a variety of controlling factors, most of which have been only inadequately described

Hyman This is probably off the point of shock, but the number of questions on it reflects the lack of clear information in the literature There has been a great deal of confusion as to the mechanism whereby these small vessels change caliber I have looked

ried out in normal rats The sample to be tested is introduced intravenously, and the alterations in the reactivity of the mesenteric vessels to topical epinephrine are then followed When blood samples are assayed, the plasma or serum is injected We have studied by the rat mesoappendix technique blood samples obtained from rats, cats, guinea pigs, dogs, and humans, with no untoward species effects on the response To my knowledge, there is no other known biological assay procedure which permits the detection of such small amounts of vasoactive material as is possible with the rat mesoappendix procedure

Moore. And the quantitative expression is 0 to 4 plus, or something like that?

Nickerson Is it possible to express these results as ± 10 per cent, ± 20 per cent, or ± 50 per cent?

Zweifach· I would like to emphasize that thus far we have not attempted to quantitate either VEM or VDM as accurately as that The precise end-point of the experiments is the minimal amount of epinephrine which will produce a vasoconstriction and slowing of the flow through the capillary bed Thus, in a selected instance, following circulatory stress, the effective dose of epinephrine may be a concentration of 1 400 million The topical application of 1.450 million will give a response which is not sufficiently pronounced to permit accurate quantitation The application of 1 500 million will give no visible reaction Under control conditions, the application of 1 4 million usually represents the threshold value Although a vasoconstrictor response can be obtained with 1 6 million, the reaction is sufficiently different to permit a distinction between these two concentrations Therefore, the average values for epinephrine reactivity which are given in Figure 3 are accurate determinations within the limits of the above variability

Nickerson If you take the sample that gives an average increase of 205-fold, and test it 10 times, what will the range be?

Zweifach In terms of the rat test per se, we do not record our data in the same way In other words, we would not say that sample A is 205 times more active than sample B The reproducibility of the rat test data has, of course, been thoroughly checked When an unknown blood sample is tested by several individuals, or by the same individual several times, the vasoactivity values check extremely well VDM activity is expressed simply in terms of the duration of the depression, that is, VDM for twenty-five or thirty minutes, as the case may be On repeated tests, a given sample will show VDM activity for twenty-six minutes, thirty-two

Burton: Perhaps I can add some quantitative studies. I have had a student for two years studying my photomicrographs, measuring the diameters of the small vessels under different heads of perfusion pressure with the circulation flowing and stopped, and I can agree with Dr Zweifach that normally they are so rigid, owing to their small size and the physics of the situation, that the distensionability to pressure alone is less than 0 1 per cent of volume change, or half of that in diameter change, per millimeter of mercury. Not until you get to the much larger vessels, 200μ or so, do you get up to 2 per cent So, you see, the capillaries act like large rigid tubes in the experiment You may say our vessels are not normal, because, being biophysicists, we deliberately use cyanide in order to remove any active tension, but the fact is we did not find any difference in the results when using cyanide and not using it in the case of the capillaries

Zweifach Changes in capillary tone are most readily brought about in adrenalectomized animals. It would therefore appear that the adrenal cortex, through its effect on intracellular electrolytes, may contribute to the maintenance of endothelial cell tone

Burton· Would you say that the tissues around the capillaries do not contribute at all to this phenomenon?

Zweifach· No, I simply say that the endothelium possesses what I call intrinsic tone

Burch· Do you believe the tightness of the tissues supporting the endothelium on the outside influences the phenomenon?

Zweifach The capillary endothelium is closely enmeshed in a pericapillary sheath which appears to be a condensation of the surrounding connective tissue To what extent the rigidity of this sheath limits or interferes with the changes in caliber of the capillary wall is difficult to say In a nonparenchymatous tissue, such as the mesentery, the pressure exerted by changes in the extravascular structures has only a minor effect on the caliber of the capillary. One might anticipate, for example, that with edema and an increase in interstitial pressure there would occur a narrowing or collapse of the capillaries In skeletal muscle, shortening of the striated muscle fibers during contraction deforms the capillaries and almost obliterates them This is the only situation in which I have observed extravascular phenomena to affect physically the caliber of the capillaries

Moore There is no species effect that you are testing in the dog's or the guinea pig's blood?

Zweifach The assay procedure for vasoactive substances is car-

Zweifach We can arrange blood samples in a relative sequence with respect to their vasoactivity. I believe that is as far as the rat assay procedure can go, using single samples.

MESOAPPENDIX TEST FOR VDM AND VEM

A critical aspect of our concept is the relation of blood-borne principles to the vascular phenomena which are observed in the shocked animal. The presence or absence of these humoral factors is determined by the rat mesoappendix procedure. I should therefore like to scrutinize the validity of the rat test per se. In the first place, the assay of samples by this procedure is made as objective as possible. The particular samples are numbered and the person doing the assay procedure is not aware of the nature of the sample. The end-point which is followed, that of a vasconstriction of the metarterioles and precapillaries sufficient to slow or stop the blood flow, is easily recognized and noncontroversial. However, there is a good deal of skill involved in making the preparation and, on the basis of past experience, being able to recognize a poor preparation. During the past ten years we have carried out over twenty-five thousand assays with this technique. The studies have included shock produced by a wide variety of experimental procedures. Early in our studies, during World War II, when some skepticism was voiced as to the reproducibility of the rat test data, we did a series of so-called blindfold tests in conjunction with the group under Dr. Magnus Gregerson. This data has been published (15) and in every instance where fatal shock ensued in the dog following leg pounding, the same sequence of an initial liberation of VEM and a subsequent elaboration of VDM into the blood was present. In several instances where VDM was either absent or minimal, the animals were found to have developed only a mild state of shock and survived. Several other such studies with unknown blood samples were done in collaboration with Dr. P. Nastuk and Dr. W. Walcott on irreversible hemorrhagic shock in unanesthetized dogs. These involved frequently as many as five to six samples of each animal. In no instance was the rat test data out of line with reference to the sequential changes during the progression of shock.

We have found that different individuals testing the same samples will, in over 90 per cent of the cases, find the presence or absence of the same type of vasoactivity. The differences which appear are referable to a more precise quantitation of the activity, on the basis of the duration of the effect or the intensity of the change in reactivity in terms of the amount of epinephrine required to produce

minutes and twenty-nine minutes VEM activity is usually titered both on the basis of the duration of the effect and the amount of epinephrine required to reproduce the threshold vasoconstrictor response. Thus, a given sample would be designated as VEM for thirty-five minutes [4x], the 4x in the brackets indicating the number of times that the original concentration of epinephrine had to be diluted in order to reproduce the control vasoconstrictor response In this specific instance, the control response was obtained with 1.4 million of epinephrine After the intravenous injection of VEM, at the height of the increase in reactivity, a threshold response was obtained with 1.16 million, a fourfold dilution When VEM is quantitated in this way, we encounter somewhat greater variability than with assay of VDM, both in duration of the vascular effect and in the number of gamma of epinephrine required to produce a control response. We have thus far not attempted to compare the relative activity of several samples, other than to say that one sample has a great deal of activity, another has moderate activity, and a third has little

Moore But the point is that you don't grade VEM and VDM on a quasiquantitative basis It is either present or absent

Zweifach. It is possible to plot a curve of vasoactivity using as the abscissa the gamma epinephrine required to produce a vasoconstrictor response, and as the ordinate the duration of effect in minutes The base line for such a curve remains comparatively stable, since only minimal fluctuations in reactivity occur with a saline sample or without introducing a test substance intravenously The advisability of attempting to quantitate the activity of different samples on the basis of individual rat test assay curves is a question which cannot be adequately answered at present Certainly, the same sample, repeatedly assayed in different rats, will give essentially the same type of assay curve with a range, at most, of plus or minus 25 per cent in either the duration or the intensity of the effect

Moore And you assume that that is a linear function or an inverse linear function of the amount of VEM present?

Zweifach I do not feel that rat mesoappendix assay curves can be used to titer quantitatively the VEM which may be present in an unknown sample

Moore That is what my question is related to Can you take a series of bloods and come out with all of them having the same amount of VEM or having more or less VEM, and if so, how much?

elaboration of VEM and VDM in a very regular fashion during the shock syndrome.

The question has also been raised, from time to time, whether the rat test for VDM may be measuring not a specific substance but merely an effect which can be produced by a wide variety of nonspecific tissue derivatives.

Shorr: Would you explain the important evidence which is provided, with respect to the specificity of the rat test, by our combined use of the test and antiserum to ferritin?

Zweifach: I believe the procedure which we routinely employ for a more complete assay of blood samples by biological fractionation clearly indicates the specificity of the rat test for VEM and VDM. Blood samples from normal individuals give a neutral rat test. The possibility existed that under different conditions both VEM and VDM could be simultaneously present in the blood stream so as to interfere with the specific vascular effects produced by each principle alone. Two procedures have been adopted to fractionate selectively blood samples. Our initial studies showed that normal kidney tissue possessed the capacity to inactivate VEM under aerobic conditions. Such an incubation did not affect VDM. It was therefore possible to wipe out the VEM titer of a particular sample by incubating the plasma with slices of normal kidney tissue (5 ml. plasma to 1 gm. kidney tissue) for a period of one hour at 37.5° C. This served to unmask the precise titer of VDM which was present. In addition, the identification of VDM as the protein, ferritin, made it possible to develop antibodies to ferritin. When a blood sample showing VDM activity in the rat test was incubated with a small amount of antiferritin serum, the vasodepressor activity of the sample was completely abolished. Incubation with antiferritin serum of blood samples containing both VEM and VDM destroys the VDM activity and reveals the precise VEM titer which is present. Biological fractionation not only aids in the more exact evaluation of VEM and VDM activity in a given sample but indicates that the vasoactivities of biological material are due to specific principles.

Haley: We are unable to inactivate VDM or recrystallized dog or horse ferritin *in vitro*. One day the sample is inactivated, then a technician gets it under another code number the following day, and it is active.

Moore: You mean having been treated in the same way?

Haley: Yes, the results are variable despite the use of anti-rat, anti-horse, or anti-dog antiferritin. Our *in vitro* experiments have had us so puzzled that we do not know what the answer really

the standard control response. I am including in this presentation a graph (Figure 4) showing the reproducibility which it is possible to obtain with the rat mesoappendix technique The data refer to a given sample of ferritin which has been tested by different individuals over a period of many months. The reproducibility is equal to that of other biological assay procedures.

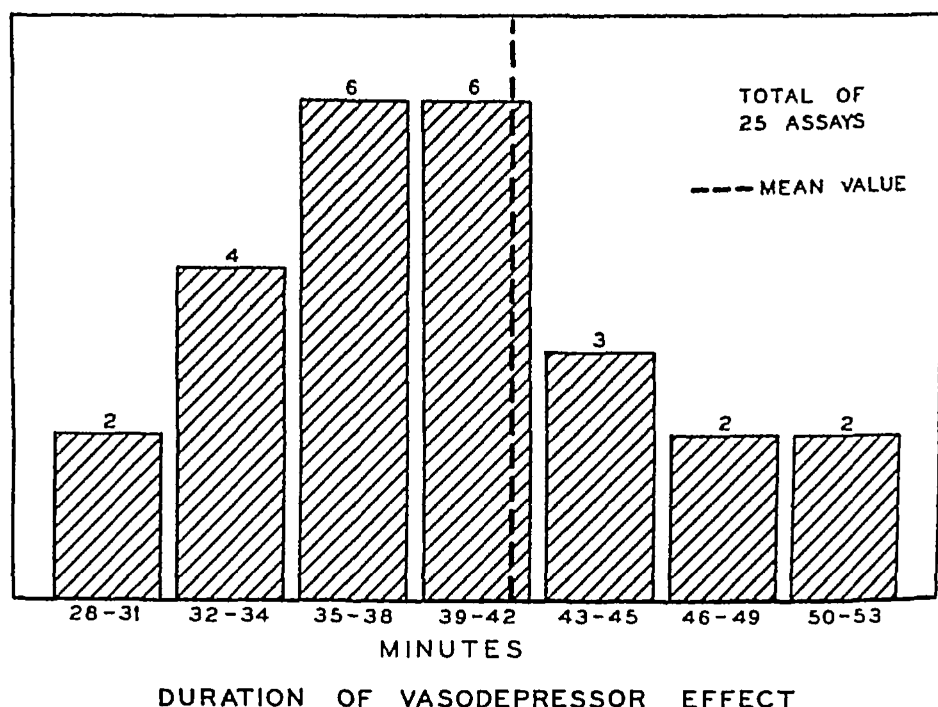


FIGURE 4 Activity values obtained when a given sample of crystalline ferritin (E-1324) was repeatedly assayed by the rat mesoappendix procedure by three different testers over a period of 18 months The vasodepressor activity of each sample is expressed as the length of time during which the metarterioles and precapillaries remained refractory to a minimal effective dose of epinephrine, e g, VDM for 32 minutes The frequency distribution of 25 separate assays are plotted in the above bar graph, the number of cases in each category being indicated above each bar

Our inferences on a causal relationship between the presence of these blood-borne principles and specific vascular alterations in the shocked animal are still based on incomplete data However, I believe that the rat test data are sufficiently extensive and valid to provide a challenge to any skeptic to consider their implications in a particular concept of shock It is not possible to dismiss the rat test data as epiphenomena without offering an explanation for the

bed in series or in parallel Secondly, the role of the anastomoses, which are so prominent in the mesenteric bed, as has been nicely shown by Bentley, is very different from that of anastomoses elsewhere Hemodynamics show the presence of these anastomoses (Figure 5) beautifully in the mesentery For the rabbit's ear, where so much is heard about anastomoses, the curve is quite different

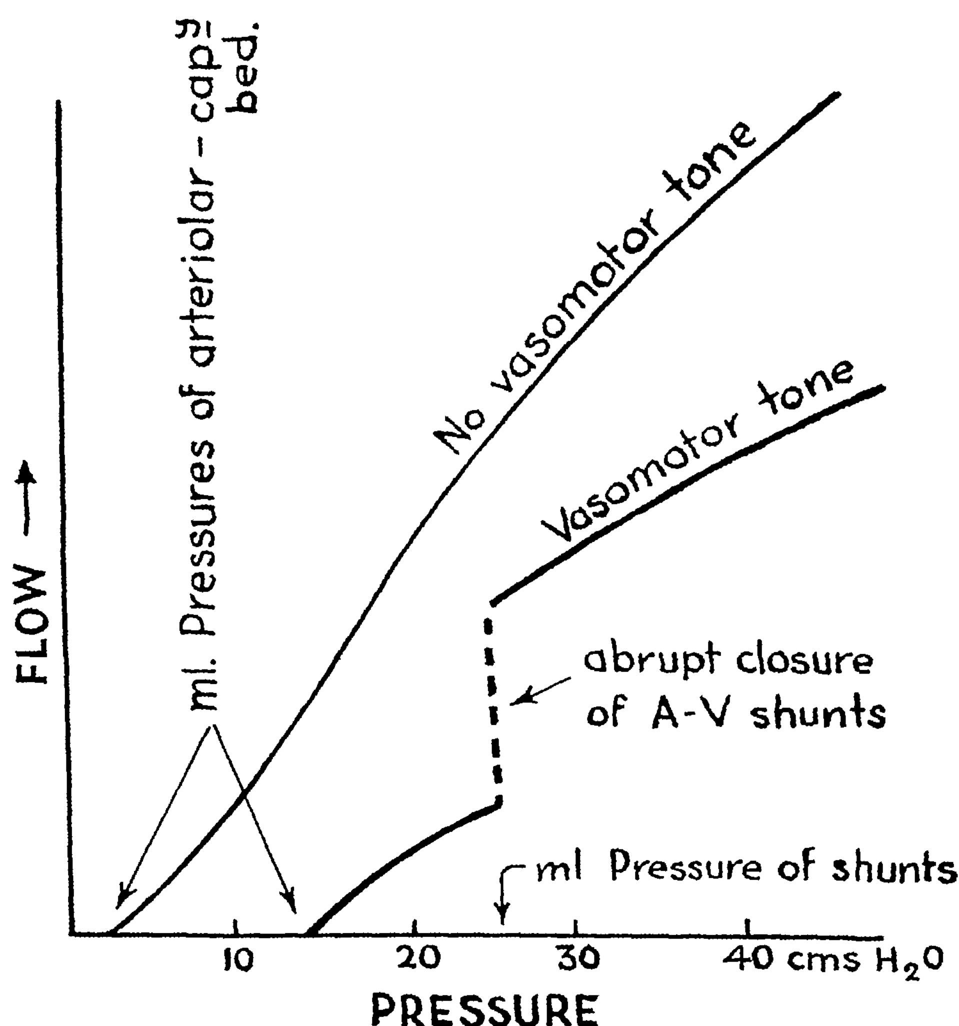


FIGURE 5 Type of flow-pressure curve found in the perfused mesenteric bed of the frog When vasomotor tone is present, as indicated by the increased final critical closing pressure (where curve hits axis), there is an abrupt break, which is interpreted as a separate critical closure of the arteriovenous anastomoses

Thirdly, we are beginning to get some evidence about the vascular reflexes of the mesenteric circulation This is work that Scarborough started with Landis, and it is being carried on by Grayson (16) Their work indicates that when you cool a man, his mesenteric circulation decreases, whereas skin circulation increases

is. But consistently *in vivo*, if we give the ferritin first, we can knock out the vasodepression, or if we give the antiserum first, we can prevent it and at times unmask a small amount of VEM activity We have also done the same thing with inactivated serum We can inactivate it by aerobic incubation and then reactivate it by the addition of cysteine, and then knock out the activity with antiserum. The thing that is puzzling us is why won't it work *in vitro*? Maybe you have an answer.

Zweifach: Dr. Mazur has been able to inactivate ferritin *in vitro* with antisera I cannot explain your inability to do so. We have found it preferable to assay blood samples as soon as possible after they have been drawn. The samples are stored immediately in ice and, when kept chilled, will maintain both VEM and VDM activity for at least several days. Thereafter the activity begins to deteriorate.

Haley: We find that by freezing our samples we can preserve them for periods as long as three months.

Zweifach: We have not made a systematic study of the stability of blood samples which have been frozen and kept refrigerated for extensive periods of time.

Franklin: This was VEM?

Haley: VDM. I would not want to hazard a guess on VEM, because I really don't know.

Burton: Perhaps this is going back from the particular to the general, but I should again like to raise some of the criticism that was expressed earlier. It seems to me that if we accept what Dr Zweifach has seen in the mesentery, the critical point is whether or not we can accept the mesentery as a representative vascular bed. Of course, the existence of VEM and VDM stands upon a different ground. That does not depend on whether we think the mesenteric vasculature is representative But whether or not the changes which VEM and VDM evidently produce in the mesenteric circulation mean that VEM and VDM are important at all in the picture of shock in the whole animal will depend on whether or not we consider it representative It is most unfortunate that the mesentery is the vascular bed that we can observe under the microscope most easily, since I think it is perhaps the most unrepresentative of any bed. The reasons, very briefly, are these First of all, obviously we are dealing with a double vascular bed, or two vascular beds in series — the portal and the mesenteric Moreover, the mesenteric is shunted by the spleen. So that what you see happening in the mesenteric circulation, from the hemodynamic point of view, might be completely reversed by what is happening in this other

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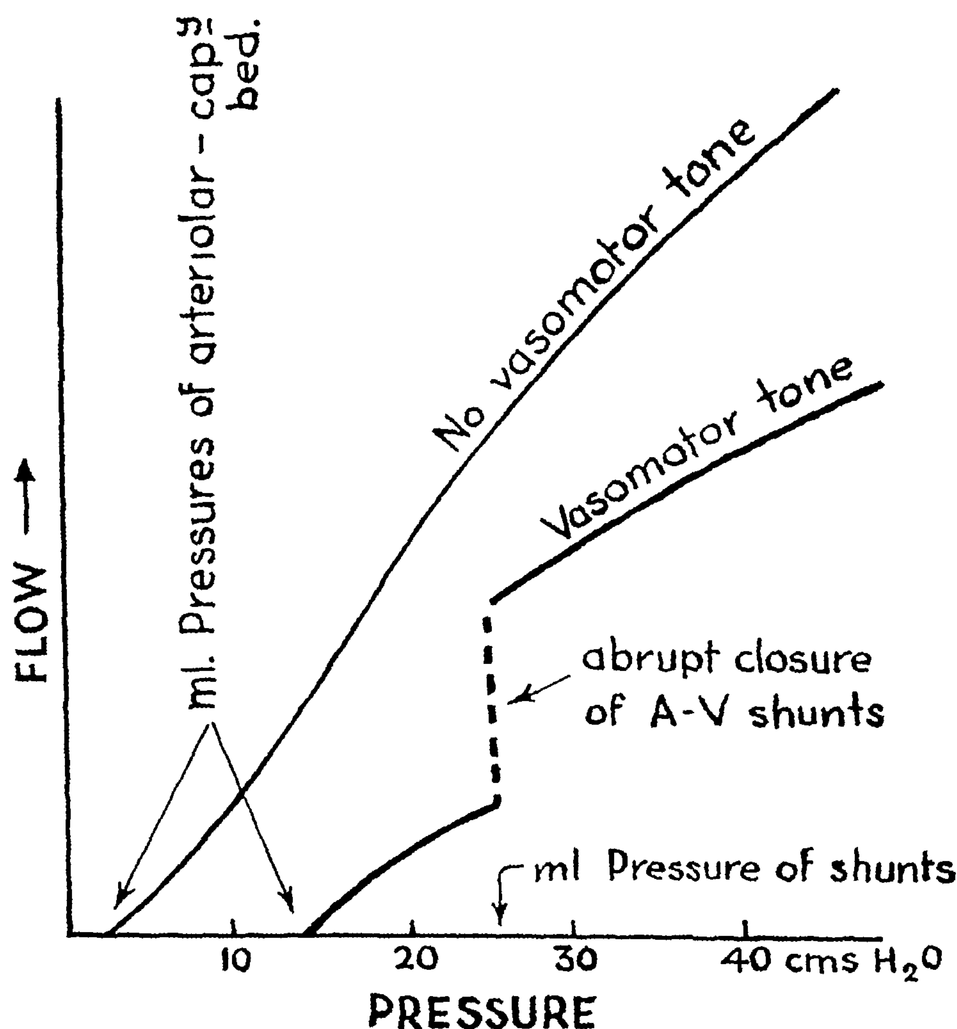


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You have made the statement that by far the most important things controlling the circulation of the terminal vascular bed were the humoral ones, but you yourself contradicted it when, in dealing with the whole animal, you showed the striking effect of sympathectomy I think it is very possible that in the mesenteric circulation the vasomotor component, meaning by that the neurogenic component, is very minor, but in other vascular beds it may be very important indeed

Finally, I am unable to find in the mesentery of a frog any reactive hyperemia. I don't know if this is general

Zweifach· Oh, you can get that A reactive hyperemia can readily be demonstrated in the mesentery or omentum Limiting factors in such experiments are the failure to exteriorize the mesentery for observation with a minimum of trauma and to maintain the tissue under rigidly controlled conditions

Burton· However, it is very marked elsewhere In view of all this, it does look as though it was most unfortunate that we have chosen this particular bed to generalize from

Zweifach I do not believe that the objections which you have raised are directly relevant to the significance of the omental and mesenteric data to the over-all shock syndrome We have not attempted to generalize from the circulatory changes in the mesentery to specific disturbances in other tissues However, there is good reason to believe that the general pattern of the sequelae in the mesentery reflect the vascular behavior in other visceral structures

Burton. This does not affect your argument on VEM or VDM, which stands or falls upon the assay I don't know whether I express the doubt of some other people, but I am very much bothered by the fact that in the whole of this assay method, which again is on this particular specialized circulation, you have to use topical application To me, you see, that seems so far from the physiologic case I would be very much happier if you could do your assay by means of the perfusate

Zweifach· We did

Burton What happens when you use the perfusate?

Zweifach Same thing

Burton Why do you have to use the topical application?

Zweifach Actually, I think topical application, rather than intravenous, is closer to what we are interested in

Burton Physiologically, does it have any relevance to anything?

Zweifach It may not be epinephrine that is released at the tissue nerve endings but a substance such as sympathin, which is released

onto the surface of the muscle cell

Moore I should like to put a plug in for the stimulation it has been to us on the clinical side to have these concepts introduced Yet I should like again to ask some questions about the assay method because I am puzzled about its significance In this assay, the test animal is not in shock or anything that even resembles shock In your assay technique, isn't it simply a normal rat under a microscope?

Zweifach Yes

Moore And both VDM and VEM are measured in shocked dogs by taking the dog's blood and injecting it intravenously into the test animal while that animal's mesentery is under observation Is that correct?

Zweifach Yes

Moore And the recipient animal in this bioassay is a normal animal as nearly as you can determine except for the minor operative procedure of getting the mesentery out?

Zweifach Yes

Moore And then it is the alteration in the reaction to locally applied epinephrine that determines the titer of the VEM and VDM?

Zweifach Yes

Fremont-Smith Its significance would depend on the degree of predictive value it would give, irrespective of whether it had any relationship to the shock in that animal As a matter of fact, it was in our first Shock Conference, held here in the Beekman Hotel in 1940, that Gregerson suggested that he would like to send down some of the blood of his traumatized dogs As he mentioned earlier, Dr Zweifach was able to predict whether the animal did in fact recover from transfusion or not by the way the normal rats' and tested rats' mesenteries reacted to intravenous slugs of the blood taken from the dog Therefore, it seemed to me that this had validity in the sense that it lent predictability But if it could be done with a spectrometric flame, it would be exactly as significant It happens to be a convenient method of getting a prediction

ACCURACY OF THE MESOAPPENDIX ASSAY TECHNIQUE FOR VDM AND VEM

Moore I should like to see some data for the assay technique on reproducibility, on stability, on quadruplicate and quintuplicate determinations, as unknowns, and all the other things which we who are chemically minded would immediately set up if we were

developing a new isotope technique for total body sodium or something like that

Short May I call on Dr Haley instead of Dr Zweifach, because it would be of interest to hear the experience of another laboratory

Haley The amounts of VEM we found in radiation were infinitesimal compared to what Dr. Zweifach finds in shock However, the amounts of VDM can actually be titrated

There is a range of VDM activity (see Table II) The gammas of horse ferritin nitrogen equivalents in Table II are based upon the figure 0.0005 gamma That amount of ferritin will give a consistent depression of the mesenteric capillary bed, so that the amount of epinephrine required to get a reaction would be around 1 in 100,000 Sometimes we have gone down to 1 in 60,000 The peripheral vasodepression can consistently be demonstrated when this amount of ferritin is given intravenously to test animals

On that basis, we took 0 5 ml of plasma from irradiated rats, injected it, and found a vasodepression We then took smaller amounts of that plasma and diluted it with normal saline, which, incidentally, has no effect upon the peripheral vascular bed, and arrived at the figures given in Table II In other words, there was more than 0 1 gamma but less than 0 5 gamma, or, in equivalent vasodepressor doses, the range was between 100 and 500 for the first series In the second series, it turned out to be 2 and 10 for the first sampling day, with a slight rise on the second day

TABLE II

Estimated Amount of VDM Liberated by Radiation Pooled Plasma Samples from 5 or More Irradiated Rats

RAT VDM	Days Post-Irradiation		
	1-2	3	4
γ Horse Ferritin N Equivalents	Nil	(1) 0 10 - 0 50	0 012 - 0 048
		(2) 0 002 - 0 01	0 040 - 0 20
No of Just Vasodepressor Doses/ml Plasma	Nil	(1) 100 - 500	12 - 48
		(2) 2 - 10	40 - 200

One vasodepressor dose equals 0 001 γ horse ferritin N/ml Reprinted, by permission, from Haley, T J, *et al* Presence and identity of vasotropic substances in blood of rats subjected to acute whole body roentgen ray irradiation *Am J Psysiol* **168**, *628 (1952)*

Moore Is there something in Table II which answers the question of reproducibility and accuracy?

Haley The Table is drawn on the basis of showing that you can titer out the quantity, and we have been able to reproduce a given figure on a given sample of plasma In other words, the one that showed from 100 to 500 vasodepressor doses could be duplicated the following day Furthermore, we can do that consistently

Nickerson. You are assuming a 400 per cent variation in your titer

Haley Yes, on the basis of those figures, because we have not felt it worth while to get the results any more exact However, we could do so

Fine What is this radiation of rats?

Haley X-radiation

Fine Were these rats sick and did they recover from radiation?

Haley These rats were in the first week, and the downward response represents the increasing amount of epinephrine required to get a reaction It has been demonstrated that the decrease, particularly during the third to the fifth day, is produced by VDM, which we have identified as ferritin by Dr Shorr's and Dr Zweifach's criteria

Fine Is this intended to simulate some kind of shock syndrome?

Haley That, Dr Fine, is a very good question It has puzzled me considerably We find in this case the sequence of VEM-VDM is the reverse of what we get in shock The VEM does not show up until the second week

Moore Well, after all, we were getting into this purely from a chemical point of view Can you take a flock of samples and put them through this bioassay, coming out with a curve that will give a mean and a frequency distribution on which a standard deviation can be calculated?

Zweifach There are several alternatives with regard to a more accurate quantitation of the rat assay procedure A given sample can be tested several times in different animals We have found that this is not necessary if one is interested merely in learning whether sample A or B has a particular type of vasoactivity and if one is satisfied to designate the activity in terms of +++, ++, or + In instances where more precise data are desirable, the following procedure has been adopted Serial dilutions are carried out on a given sample, the dilutions being done until vasoactivity disappears On the basis of this simple procedure, sample A will be considered to have greater vasoactivity than sample B if 6 dilutions are required to wipe out the activity of A as compared with only 4 dilutions in B In addition, one can plot the curve of relative

vasoactivity at each step in the dilution procedure Unfortunately, we found that the relative vasoactivity, with change in concentration, does not show a linear function (even when plotted on a logarithmic scale) For example, serial dilutions of a given sample of ferritin, starting with the high concentration range, show first a flat curve of vasoactivity, then a sharp fall in vasoactivity, and when the lowest effective concentrations were reached, again a flat curve This gives us an S-shaped curve Obviously, if the initial concentration of ferritin in a given sample falls on that portion of the curve which has a sharp slope, successive dilutions will show a rapid falling off in activity On the other hand, concentrations which fall on the flat slope of the curve will show a more gradual falling off in activity on dilution It is for this reason that unknown biological samples, such as blood or interstitial tissue fluid or tissue extracts, are difficult to quantitate in terms of units of vasoactivity. It is possible, by doing sufficient numbers of tests on a given sample of blood, to prepare a dilution curve which resembles, for example, that obtained when a solution containing 0 005 gamma of ferritin per ml is subjected to comparable serial dilution and assay

Moore But you don't attempt to quantitate it any closer than that?

Zweifach No

Shorr Could I summarize the tenor of the questions with respect to VDM or VEM as follows to what extent can this test be considered to have the accuracy that we demand of a chemical procedure? The answer is that it does not have the accuracy of a chemical procedure which we require to be plus or minus 2 or 3 per cent, but that it is the experience of our own laboratory and of Dr Haley's that one can differentiate clearly and reproducibly between no VEM or VDM, and between mild, moderate, and profound effects

Zweifach I think it is unfair arbitrarily to discuss the rat assay data in terms of percentages We should consider the fact that the assays are dealing with concentration ranges of 0 001 to 0 005 gamma of ferritin per ml Although 0 001 represents a 500 per cent change with reference to 0 005 gamma, we actually are working in a narrow range of physiologic activity

Moore I am not sniping I am not being critical I am just asking for information You have a bioassay All I am asking is, how much of an assay is it? Just plus or minus some per cent would answer my question.

Haley I don't think you can take this assay as you would an epinephrine assay and come out with a standard error of plus or

minus 3 per cent. I would never want to say that you could do that, but I would say that the range over which you can detect these responses is rather large and, for a given sample, the work can be duplicated

Nickerson Is it correct to assume that at this stage of development, if this test is quantitated, we may assume a possible error of about 200 per cent?

Zweifach It would depend on the specific feature of the assay procedure to which you are referring

Nickerson. In using the dilution technique, when one level can be detected, then the question is how much must the change from that level be in order to be sure that there is a difference? The minimum detectable difference is, of course, the final criterion of the sensitivity of the method. How consistently that can be reproduced is a measure of the accuracy of the method I gather that the differences which are detectable are of the order of magnitude which I mentioned. That is, you could not determine the difference between 0 001 microgram of ferritin and 0 002 microgram, but you could detect the difference between 0 001 and 0 005 microgram. Am I correct in this interpretation?

Zweifach I do not believe that we can readily distinguish between 0 005 gamma of ferritin and 0 001 without doing a large number of single assays and serial dilutions on the test sample The precise quantitation will again depend on the range of concentration which the particular sample has This is a difficulty which is encountered because of the S-shaped character of concentration-activity curves of VDM and VEM

Nickerson If you are using a dilution technique, the range in which you start should be unimportant You simply dilute it more times before getting to the critical point of determining between one sample and the next That is where the final evalution occurs The question is how much difference does there have to be between those two samples in order to get a detectable, reproducible difference in the test? I gather from the discussion that if this difference is on the order of one to, at a maximum, five times, you can be quite sure of it If we must speak in per cent, which always makes it sound bad, this is a difference of 100 to 500 per cent

Shorr As you say, if we attempt to deal with the data obtained in the mesoappendix test by statistical methods, it does sound bad as far as accuracy is concerned But I think that this is the wrong way of evaluating the information which this test can give We have on the one hand a negative reaction, and on the other hand

we have positive responses of varying degrees of intensity which we know are obtained with the injection of between 0 0005 to 0 001 μg of ferritin N Inasmuch as ferritin is never present normally, but only under pathologic conditions, the mere presence of a positive test is significant Additional significance is acquired by the intensity of the vasodepressor reaction which can be graded as mild, moderate, or strong It is only the order of magnitude that is of importance, and to attempt to arrive at a quantitation beyond this order of magnitude by statistical methods is unwarranted

Fremont-Smith The significance would be in relation to the significance of the difference detected The importance of the error does not lie in what the percentage of error is in the numerical figure, although that is a way of characterizing it, but as to what it will do In other words, how pertinent is the change that is detectable to the particular problem which is being studied Isn't that right?

Nickerson The point to which the study of VEM and VDM in shock has been carried by Drs Shorr and Zweifach and by others indicates that the test is sufficiently sensitive to provide useful data No one will argue that point

Fremont-Smith I think that it has been argued That is exactly the issue under discussion In fact, it needs to be argued for the very reason that there is considerable doubt, particularly in the minds of people who have not examined the situation, as to how useful the information can be

Nickerson The fact that ferritin reduces vascular reactivity is useful information, but I think the question of whether this has anything to do with shock or hypertension is a very different question from that which we are talking about now, the question of how accurately one can determine ferritin

Moore I think Dr Shorr answered it a minute ago about VEM You can have a little, or quite a bit, or a lot And that is about it

Shorr Does one need more in terms of the descriptive relationship between these factors and the sequence in shock?

Moore No, but I think it is nice to know that that is the sort of bioassay you are working with

Burch Is the bioassay influenced by the solvents, normal saline, and plasma? In other words, does plasma possess a substance that alters the bioassay?

Haley Not that I know of

Franklin Are you any nearer to finding out the chemical nature of VEM?

Shorr: No, not very much nearer.

Fremont-Smith: May I make a comment on what I think I have observed in the group, as well as at other times in arguments with individuals, that is, as I go along and try to make my point, not what I am saying at that moment but what it might lead to is such a dangerous thing to the other person that he finds it quite necessary to block me, to challenge a whole series of statements I am making. Actually it is not a challenge, it is an expression of anxiety as to what might follow if he allowed the first statement to go by.

I think it was quite clear, if we really listened to Dr. Zweifach, that he was trying to set a frame of reference within which he was going to describe some fairly specific experiments. The frame of reference, really, was the thing that disturbed many, because we couldn't be quite sure what would come out of it afterwards. It is rather interesting to do a little observation on ourselves in this experiment in communication.

PERIPHERAL VASCULAR REACTIVITY IN SHOCK

Zweifach: In broad terms, the changes in the peripheral vascular bed of the omentum permit the recognition of two phases during the development of shock, irrespective of the initiating factor. There is an initial period, during which the vascular readjustments are compensatory in nature and all phases of peripheral vascular activity become augmented. The extent to which compensatory readjustments develop depends, of course, upon the precise conditions of the experiment and the nature of the initial insult.

A specific protocol used to characterize the vascular changes during the compensatory stage is a case of hemorrhagic shock carried out under pentobarbital anesthesia (Figure 6). The same two phases of vascular response are seen in the different types of experimental shock which we have studied. These include tourniquet shock in dogs and rats, drum trauma shock in rats, and leg pounding shock in dogs. In a given experimental situation, the degree to which the various compensatory or decompensatory phenomena develop depends upon contributory factors referable to conditions peculiar to each experiment.

Anesthesia represents an important contributory factor to the development of the syndrome. Shock has been produced in laboratory animals under general anesthetic agents, such as pentobarbital, pentothal, ethre, or cyclopropane. In another group of experiments, morphine was used in small doses sufficient to produce a

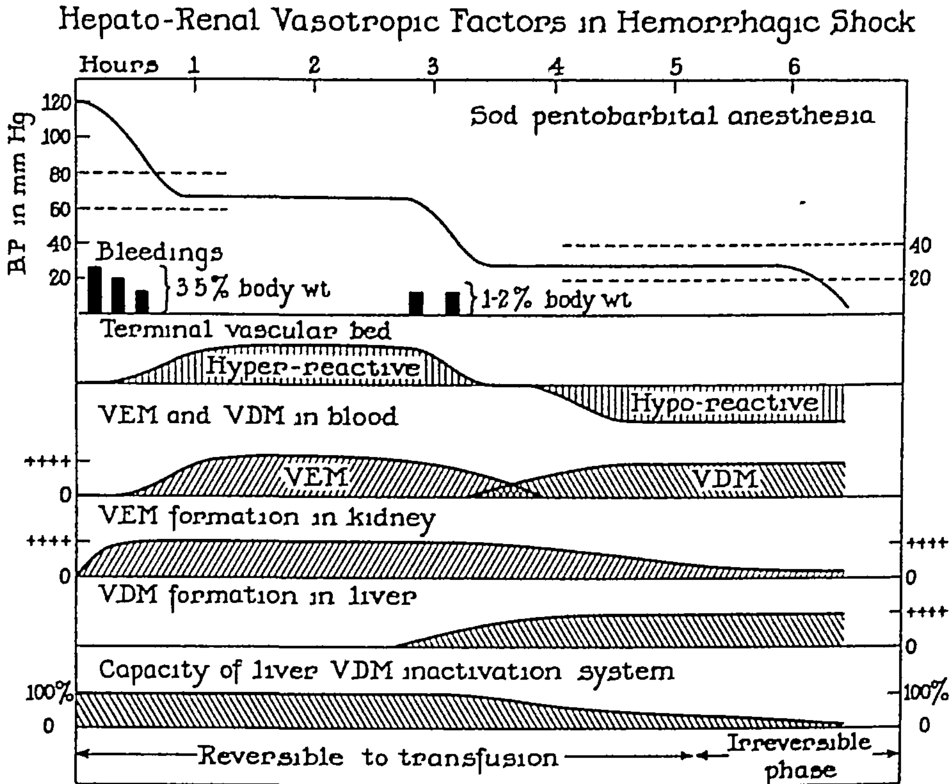


Figure 6 Schematized protocol of sequence of vascular and humoral events following graded hemorrhage Compensatory response of capillary bed (hyperreactivity to topical epinephrine and augmentation of vasomotion) is associated with elaboration of VEM into circulation by kidney Capacity of kidney to form VEM becomes progressively impaired with presistence of hypotension and prolonged renal hypoxia Decompensatory vascular pattern (hyporeactivity to epinephrine and suspension of vasomotion) associated with elaboration of VDM (ferritin) into blood by hypoxic liver Continued formation of VDM by liver is related to impairment of hepatic enzyme mechanisms for inactivation of vasodepressor Irreversible phase of syndrome characterized by vascular decompensation and deterioration of VDM mechanisms in liver Reprinted, by permission, from Shorr, E , Zweifach, B W , and Furchgott, R F *Research in Medical Science* New York, Green, D and Knox, W E , editors, The Macmillan Co , 1950 (p 323)

euphoric state A small group of experiments were done with local infiltration of the wounds with procaine to permit exteriorization of the omentum and insertion of the blood pressure cannula In all of the above experiments, the same two sequences of vascular response developed to varying degrees In most instances, anesthesia served as a predisposing factor which limited the compensatory response and hastened the onset of decompensatory reactions Experiments in dogs with no systemic anesthesia demonstrate that these animals are much more resistant to the development of decompensatory vascular activity when subjected to conventional experimental procedures However, by using more drastic procedures,

such as the maintenance of the blood pressure following hemorrhage at levels below 30 mm Hg for protracted periods of from three to four hours, vascular decompensation in the omentum can be achieved

Moore And these occur even under high spinal anesthesia?

Zweifach We have not carried out shock experiments in animals under spinal anesthesia In the anesthetized dog, the compensatory phenomena persist for a variable period of time, during which different aspects of vascular response become less effective and may actually become subnormal This latter portion of the syndrome is referred to as the decompensatory stage and is characterized by the progressive development of subnormal or hyporeactive responses within the terminal vascular bed The development of the hyporeactive phase usually presages collapse of the circulation and is invariably associated with a failure to respond to blood replacement measures This is in contrast to the excellent prognosis with respect to recovery by blood transfusion during the initial compensatory phase where the replacement of the blood, withdrawn during the experiment, rapidly restores the circulation

Thus far, the major generalization which has been drawn is the development of an initial compensatory and a subsequent decompensatory vascular pattern in all types of shock, irrespective of the initiating factors We have not considered specific factors which will alter the compensatory pattern It is a common observation that experimental animals differ in their response to small blood loss This is conditioned by the nutritional status of the animal, the presence of infection, the state of hydration, and other metabolic or humoral disturbances which may be present Some of these variables have been subjected to experimental study and will be discussed later

RELATIONSHIP OF VEM AND VDM TO VASCULAR DERANGEMENTS IN SHOCK

Our studies have shown that the regulation of blood flow through the peripheral vascular bed is in large part dependent upon humoral factors We therefore attempted to relate the vascular changes observed in the omentum of the shocked animal to the possible elaboration of humoral principles It was found that two vasoactive principles could be detected in the blood stream of the shocked animal During the initial compensatory stage of shock there appeared in the circulation a vasoexcitor principle, VEM, which in test rats produced changes in vascular reactivity and vasomotion strikingly similar to those seen in the terminal vascular bed of the

shocked animal at this time The injection of a blood sample taken from a shocked dog during the compensatory stage produced in the test rat an increased reactivity of the metarterioles and precapillaries to topical epinephrine, as well as an augmentation of spontaneous vasomotion During the decompensatory stage of the syndrome, the blood was found to contain a vasodepressor principle, VDM, which produced diametrically opposite effects on the reactivity of the terminal vascular bed. The response to epinephrine in the test animal was blunted and often abolished Vasomotion was diminished and frequently an over-all hyperemic circulation appeared in the capillary bed of the test rat. The hypothesis was then advanced that these two principles were components of a homeostatic mechanism which participated in the regulation of peripheral blood flow and which, during the circulatory stress of the shock syndrome, appeared in exaggerated form The active participation of the terminal vascular bed in circulatory hemodynamics is influenced in large part by these principles

The evidence for a causal relationship of these blood-borne principles to specific vascular derangements in shock remained largely circumstantial until this was buttressed by related studies dealing with the surgical and chemical ablation of different homeostatic mechanisms Although the implications with respect to the irreversible aspect of the shock syndrome are still inferential, the regularity with which they appear strongly supports a causal relationship

In Table III are listed different humoral factors, or so-called toxic factors, which have been implicated in the shock syndrome Such a list can be considerably expanded to include numerous parameters, related to tissue metabolism, which show a disturbance during the progression of shock One must, however, insist that changes in particular agents be referred to specific hemodynamic alterations Unless this can be shown to exist, the causal relationship of any of these humoral factors must remain purely speculative Thus far we have been unable to find tissue metabolites, other than VEM and VDM, whose presence in reasonable concentrations will produce, in test animals, the pattern of vascular changes which are observed during the development of the shock syndrome

VASCULAR DECOMPENSATION AND VDM

With the prolongation of the shock syndrome, vascular decompensation develops, primarily in the splanchnic viscera, and results in the collapse of the circulation The problem which confronts us with respect to this phase of the syndrome is whether the circulatory

TABLE III

Humoral Factors in Shock

DELETERIOUS PRINCIPLES	
Histamine	(Cannon & Bayliss, Dale & Laidlaw)
H–Substances	(Lewis, Moon)
Acetylcholine	(Dudley)
Bacterial Products	(Abraham, Aub *et al*, Fine)
Adenosine Compounds	(Bielschowsky & Green, Kalckar & Lowry)
Kallikrein	(Hastings *et al*)
Potassium	(Kerr, Scudder, Fox)
VDM (ferritin)	(Zweifach & Chambers, Shorr, Baez & Mazur)
Anaerobic Intermediate Metabolites	(Wilhelmi & Long, Allison, Henderson)
CO_2, pH	(Henderson)
COMPENSATORY PRINCIPLES	
Adrenal Cortical Secretions	(Swingle)
Renin, Sustained Pressor Substance	(Collins, Braun-Menendez, Helmer & Shipley)
VEM	(Zweifach & Chambers, Shorr, Baez & Mazur)

Numerous biochemical and humoral alterations have been shown to occur during shock However, with the exception of VEM and VDM, none of these have been related to specific vascular episodes during the progression of the syndrome

insufficiency is directly referable to a failure of peripheral regulatory mechanisms in general, or whether it is dependent upon vascular derangements within a specific organ During the initial phase of the hemorrhagic shock syndrome, the disproportionate vasoconstriction which develops in the kidney would appear to be responsible for the appearance of VEM in the blood stream Subsequent to this, with the persistence of drastic hypotension, stagnant hypoxia develops within the liver proper, as evidenced by the marked fall in oxygen saturation of the portal vein blood (17) The local release of VDM within the liver is interpreted as an attempt to improve the peripheral circulation in the face of a drastically reduced blood flow Under normal conditions with an inadequate arterial pressure, the opening up of the arterioles and precapillaries by locally released VDM would bring about an increased perfusion of the ves-

sels in the liver parenchyma. However, the local elaboration of VDM during shock is ineffective as a measure for increasing blood flow in the face of drastic hypotension and diminished circulating blood volume Actually, under these conditions the circulation through the liver is still further reduced by the expansion of the vascular bed at this stage of the syndrome The blood which enters the liver stagnates within the liver sinusoids, possibly because it is increasingly difficult for blood to leave by way of the constricted hepatic veins The development of an increased resistance to flow through the liver is accompanied by portal hypertension This in turn will interfere with the venous return of blood from the gut The effect of inadequate venous outflow, together with local factors within the gut proper, exaggerates the decompensatory vascular changes in the liver The progressive deterioration of the peripheral circulation observed in the omentum at this stage is referable to the spilling over into the blood stream of the hepatic vasodepressor principle, VDM Thus, the ultimate collapse of the circulation is a composite of several factors, and the degree to which changes develop in each depends upon the precise experimental conditions The possibility exists that deleterious factors other than VDM may arise as a consequence of the stagnant hypoxia in different tissues and that these likewise may contribute to the vascular collapse

For purposes of simplification, I have confined my remarks during this presentation to hemorrhagic shock It is well known that the shock syndrome can be produced by a wide variety of initiating factors There is, however, considerable disagreement regarding the relative significance of the different factors which are involved The initial compensatory stage during shock produced by hemorrhage or by a form of hind limb trauma is the consequence chiefly of a reduction in blood volume I do not distinguish here between the frank loss of blood, such as occurs in hemorrhage, and a reduction in the effective circulating blood volume, which may be brought about by the sequestration of blood or plasma in different tissues Once a state of shock has developed, the subsequent collapse of the circulation during the decompensatory stage is referable to a further reduction in blood volume caused by the trapping of blood within the terminal vascular bed and venous channels of visceral organs, such as the gut and liver. It is significant that during this critical stage of the syndrome as little as 10 ml of blood represents the difference between life and death in a dog weighing from 10 to 15 kg

The common denominator which characterizes the different forms

of experimental shock is the profound reduction in peripheral blood flow, as visualized in the mesentery or omentum The peripheral circulation does not become curtailed, either at the same time or to the same degree in different organs of the body. Unfortunately, the level to which the blood pressure has fallen is not a reliable index of the extent to which the peripheral circulation has been reduced under different experimental conditions A great many contributing factors can impair the capacity of the vascular system to compensate effectively for the circulatory stress For example, under ether anesthesia, the lowering of the blood pressure to 60 mm Hg is sufficient to slow the capillary circulation in the omentum drastically In contrast, in a morphinized dog, a comparable effect on omental blood is not achieved until the blood pressure reaches 30 to 35 mm Hg

COMPENSATORY STAGE OF SHOCK AND VEM

Thus far, the progressive character of the shock syndrome has been discussed on the basis of the sequence of vascular changes within the omental circulation and the relation of the hyper- and hypo-reactive phases of vascular activity to blood-borne humoral principles In Figure 6, a diagrammatic presentation is shown of a schematized shock experiment The compensatory phase of the syndrome is best reproduced by subjecting the animal to submaximal bleeding (3 to 4 per cent of body weight) The blood pressure will become stabilized in a moderate range of hypotension (on the average, 65 mm Hg) VEM appears in the blood stream within fifteen to twenty minutes after the initial bleeding, and compensatory readjustments develop in the terminal vascular bed at about the same time, reaching a maximum after sixty to ninety minutes of hypotension By making saline extracts of different tissues of the body during this phase of the syndrome and testing the extracts for vasoactivity by the rat mesoappendix technique, it has been possible to demonstrate that the blood-borne VEM is of kidney origin In experiments where the kidney is excluded from the circulation, VEM fails to appear in the blood following hemorrhage (3) The potentiation of the vascular response to epinephrine is considerably blunted and much less prominent in arenal animals subjected to hemorrhage The hyperreactive response in the terminal vascular bed is a composite of several factors involving, in addition to the kidney, the sympathetic nervous system and the adrenal glands By interfering with adequate compensatory readjustments in the terminal vascular bed, the removal of the kidney predisposes the systemic circulation to the development of decompensatory

phenomena.

During the early portion of the compensatory phase, VEM elaborated in the kidney will continue to be delivered into the systemic circulation With the progression of the syndrome, renal ischemia develops to the extent that, on the basis of clearance data, no effective circulation through the kidney cortex exists (18) This factor prevents the delivery of VEM into the systemic circulation In addition, as is noted in Figure 6, with continued renal hypoxia the capacity of the kidneys to produce VEM becomes progressively impaired After a protracted period of hypotension, many kidneys show a complete loss of this capacity

Shorr Do you feel that this change is related only to time or to time plus blood flow?

Zweifach The impairment in renal VEM mechanisms probably develops from a combination of circumstances The presence of a stagnant hypoxia for a prolonged period of time represents one factor A second factor may be the loss of some suitable substrate or cofactor in these enzyme systems

Burch When you remove the kidneys and do bleeding, does the animal present the hyperreactive peripheral circulation?

Zweifach The arenal animal was brought into the discussion in order to emphasize the renal origin of blood-borne VEM The effects which surgical nephrectomy have on the progression of the shock syndrome, especially with reference to the terminal vascular bed, will be taken up in a subsequent section

FACTORS AFFECTING VDM PRODUCTION

Selkurt Since you have just said that the circulation is impaired rather soon, how can you explain this relative delay in the VDM formation? Are there any indications for it?

Zweifach The presence of VDM in a vasoactive form within the liver is the result of two separate mechanisms, the first is concerned with the formation of VDM, and the second with its inactivation or removal (2) Saline extracts of slices of normal liver possess no appreciable VDM activity When the liver is subjected to hypoxia, similar tissue extracts show considerable VDM activity In the test rat the vascular effects of exogenous VDM persist for a period of twenty-five to forty minutes and then wear off Apparently, the normal animal is capable of inactivating or removing VDM from the circulation This capacity was shown to reside in a specific hepatic enzyme system which inactivates VDM under oxidative conditions

During the development of shock, VDM appears first within the liver proper and then spills over into the blood stream. Serial biopsies of the liver were taken during the progression of the shock syndrome and were tested both for their content of VDM and for their capacity to inactivate a standardized preparation of VDM. It could be shown that, concomitant with the deterioration of the shock syndrome, the capacity of the liver to inactivate VDM likewise was reduced (3). The precise titer of VDM in the blood stream is dependent not only upon its formation within the liver, as a consequence of stagnant hypoxia, but upon its rate of inactivation by liver enzyme systems. So long as the liver VDM inactivation systems remain intact, the blood titers of VDM do not reach significant levels. During the decompensatory stage, the onset of irreversibility is associated with the almost complete deterioration of this inactivation system. Blood transfusion at this stage dilutes the amount of VDM in the blood but has no beneficial effect on the capacity of the liver to inactivate VDM. With the persistence of this defect, the liver circulation again undergoes deterioration, VDM appears in the blood stream, and circulatory collapse ensues.

Haley Isn't it true that VDM is being liberated at all times and that it is only under these conditions that you get the massive amounts of it?

Zweifach Blood samples of normal animals give a neutral assay as measured by the rat test. Biological fractionation of normal blood samples by incubation with fresh kidney slices, in order to remove any VEM which might be present, does not reveal the presence of VDM. *In vitro* studies on liver slices of normal animals likewise indicate that there is no vasoactive VDM present within the liver, and that the aerobic incubation of such slices does not result in the elaboration of VDM into the supernatant fluid. It is only when such tissue slices are subjected to hypoxia that the formation of VDM occurs. It is possible that under normal conditions some VDM is being elaborated continuously but that the inactivation mechanisms within the liver destroy the biological effectiveness of this principle.

Nickerson Do you conceive of VDM production and inactivation simply as an oxidation-reduction process or as a matter of synthesis and structural degradation?

Zweifach Dr Mazur, in our laboratory, has shown by chemical and immunochemical studies that the VDM activity of the blood and the liver is referable to an iron-bearing protein complex called ferritin (19,20). By the development of specific antibodies to ferritin, Dr Mazur has been able selectively to wipe out the VDM

activity of blood samples from animals in shock, from the saline wash of shock liver, and from VDM produced *in vitro* by subjecting normal liver to anaerobiosis He has shown that crystalline ferritin in concentrations as low as 0 005 gamma (on the basis of nitrogen content) will produce in the test rat a VDM effect comparable in degree and extent to that produced by blood samples obtained from animals in the decompensatory stage of shock Later studies indicated that the biologically active form of ferritin had free sulfhydryl groups (21) Ferritin could be rendered vasoinactive by transforming these groups into the disulfide form by blocking the sulfhydryl radical with appropriate agents The inactivation of active ferritin by liver slices was accomplished by the same type of transformation of sulfhydryl to disulfide (22) Dr Mazur found that the liver of normal animals, when frozen immediately, with the sulfhydryl content of the ferritin determined chemically, contained ferritin which was exclusively (over 95 per cent) in the inactive or disulfide form. On the other hand, shock livers, when similarly treated, had as much as 45 per cent of the ferritin in the free sulfhydryl form The transformation from the free sulfhydryl to the disulfide occurs under oxidative conditions, while the reverse occurs under anoxic conditions This type of chemical transformation, from an active to an inactive form, does not involve any synthetic processes and can be achieved by the tissues with a minimum expenditure of energy It is our thesis that the ferritin (VDM) inactivation mechanism during the progression of hemorrhagic shock becomes impaired to such an extent that blood replacement and the restoration of oxidative conditions are no longer effective in reconstituting the inactivation enzyme system

Osserman Is it possible to delay, or in any way modify, the appearance of the "irreversible" phase by administering to the shocked animal blood which has been obtained from a second animal in the initial compensatory shock phase? In other words, what happens when one gives the acceptor animal blood containing an abundance of VEM?

Zweifach The procedure which we employ to produce hemorrhagic shock involves the graded removal of blood at intervals It is obvious that all of the bleedings, with the exception of the first, are taken during the period in which the blood contains considerable amounts of VEM The pool of blood which is returned to the animal at the end of the experiment usually has a moderate VEM activity The extent to which the intravenous administration of blood with high titers of VEM would be more effective in restoring the peri-

pheral circulation has not been ascertained

Osserman Another answer to that question would depend on whether blood from an animal that had had no chance to get into the hyperreactive stage would be as successful in maintaining the shocked animal's blood supply as the latter's own blood, which presumably does have the VEM in it

Zweifach The data presented thus far have evaluated the compensatory aspect of the shock syndrome in terms of specific homeostatic mechanisms It is significant that the capacity of the systemic circulation to adapt to circulatory stress is also altered in each instance where interference with a specific homeostatic mechanism serves to impair the capacity of the terminal vascular bed to readjust Thus, in experimental situations where reversibility to blood replacement was uniformly obtained, interference with peripheral vascular homeostatic mechanisms always predisposed to hyporeactivity and to refractoriness to transfusion

We have emphasized the relation of disturbances in liver VDM metabolism to the decompensatory phase of the syndrome The stagnant hypoxia within the liver proper during shock results in a deterioration of the hepatic circulation This is accompanied by an elevated portal pressure and, in turn, by a further reduction and deterioration of the splanchnic circulation As previously indicated, the vasodepressor activity of the blood was found to be related to the presence of ferritin in the circulation.

Vasoactive ferritin has been demonstrated in both the liver and the systemic circulation during the decompensatory phase of shock, when the circulation is maintained only by virtue of supporting infusions, or in experiments with the Lamson reservoir, by the continuous uptake of blood from the reservoir It is suggested that the reversible sulfhydryl to disulfide type of chemical transformation may be a prototype of other humoral mechanisms concerned with the regulation of the blood flow Although ferritin per se may not be directly implicated, it is possible that other compounds with sulfydryl groups may be responsible for changes such as develop during reactive hyperemia and increased tissue metabolic activity

The administration of blood during the hyporeactive stage, to replace that withdrawn during the experiment, brings about a temporary improvement in the blood flow through the mesentery and liver For a short period of time, there is also a temporary dilution of VDM in the systemic circulation Despite this transient improvement in blood flow, the terminal vascular bed continues to manifest decompensatory responses and the blood stream progressively shows

an increased titer of VDM. This has been found to be referable to damage to the hepatic inactivation mechanism which, under normal circumstances, transforms active ferritin to its inactive disulfide form The liver of shocked animals during the decompensatory phase of the syndrome shows a marked impairment of the capacity to inactivate VDM The subsequent deterioration of the circulation is associated with an accumulation of blood within the liver and splanchnic viscera

FACTORS AFFECTING RESISTANCE TO SHOCK

The causal relationship between the hepatorenal factors, which we have been discussing, and the vascular response during circulatory stress, has been buttressed recently by a number of experiments In instances where specific measures have brought about an improved capacity to withstand shock, there have been parallel changes in these hepatic mechanisms in a direction compatible with their having a relationship to the development of resistance This is clearly evident in the experimental production of resistance to drum trauma Normal rats of a given age group, when exposed to drum trauma, show a statistically reproducible response For example, rats weighing between 120 to 150 gm, when subjected to 700 turns in the drum show a mortality of 80 to 85 per cent When such animals are exposed to repeated sublethal drummings, they develop a resistance to such trauma, and eventually survive even 2000 revolutions in the drum In such resistant rats, the hepatic mechanisms concerned with ferritin inactivation can be shown to have developed a resistance to the deleterious effects of hypoxia (23) In contrast to the livers of normal rats, liver slices of resistant animals can withstand ninety to one hundred and twenty minutes of complete anaerobiosis without a deterioration of VDM inactivation mechanisms There is also a compensatory augmentation of the VDM inactivation system as a result of which the livers of resistant rats can inactivate much larger amounts of ferritin at a more rapid rate than normal controls Further, Dr Baez has found that rats made resistant to drum trauma show a comparable resistance to the deleterious effects of hemorrhagic shock * In experiments with a standardized type of hemorrhage, drum resistant animals readily survive a normally lethal procedure The hepatic inactivation mechanisms in resistant animals subjected to hemorrhage do not show the usual deterioration which accompanies hemorrhagic shock in control experiments

* Baez, S, and Shorr, E Unpublished data

The importance of the renal factor for adequate peripheral vascular compensation has been clearly demonstrated by a variety of experiments in which shock was produced following exclusion of the kidneys from the circulation. This was shown both in experiments on drum trauma and hemorrhage in rats, and in hemorrhagic and tourniquet shock in dogs.

In assessing the renal contribution to vascular homeostasis in shock, it should be noted that experimental procedures, such as massive bleeding, which produce an acute fall in blood pressure bring about an immediate and profound reduction in blood flow through the kidney. Often this is of sufficient intensity to isolate completely the kidney from the circulation and thereby limit the possible contribution of renal humoral principles to compensatory readjustments. Likewise, experiments in which trauma or other painful stimuli are applied to the extremities are complicated by a considerable reduction in renal circulation even prior to the actual development of shock. In our own experiments, shock was produced by a graded series of bleedings in order to permit maximum development of renal compensatory principles. Under such conditions, exclusion of the kidneys resulted in a clear-cut impairment of the compensatory response.

In experiments on animals subjected to bilateral sympathectomy, the protective action of the sympathectomy per se is nullified by the subsequent exclusion of the kidneys from the circulation. A graded hemorrhage, which in control animals leads to a completely reversible syndrome, will, in the absence of the kidneys, result in an irreversible type of shock.

Howard: One question before you summarize. Have you studied this release of VDM and its subsequent appearance in the animal coincident with the administration of aureomycin?

Zweifach: We have not made a systematic study of the effects of hemorrhagic shock on liver VDM mechanisms in animals which have been pretreated with aureomycin or other antibiotics.

What can we conclude concerning the critical nature of these principles and their vascular effects on the shock syndrome? Do they represent epiphenomena, or are they intrinsic defects which contribute directly to the deterioration of the systemic circulation? Several workers have shown that, with the progression of the shock syndrome, the peripheral resistance which is initially elevated later falls (24,25). Our own observations on the splanchnic viscera indicate that the vasoconstriction, which develops in the larger blood vessels during shock, persists throughout the syndrome and, in most

instances, may become exaggerated as death approaches The circulation in the skin remains ischemic throughout. Whether the vasoconstriction in other tissues undergoes relaxation is not evident.

Our studies on peripheral vascular behavior have stressed the critical significance of a close integration between the functional activity of the larger blood vessels and that of the terminal vascular bed The achievement of tissue homeostasis would be impossible if this were not true Changes in the larger blood vessels must, of necessity, be accompanied by appropriate readjustments in the terminal vascular bed in order to achieve vascular homeostasis. When vasoconstriction of the larger blood vessels is exaggerated, adequate perfusion of the terminal vascular bed cannot be achieved without an opening up of this portion of the vascular tree, and vice versa, with dilatation of the larger blood vessels, readjustments in the terminal vascular bed, such as the opening of direct shunts from arterial to venule, and increased vasomotion, are necessary to ensure tissue homeostasis

It is obvious, from the multiplicity of factors involved in vascular readjustment mechanisms, that the degree to which each of these participate in a given syndrome can vary considerably, depending upon many conditioning factors In one situation, the failure to compensate adequately may be the predominant factor related to the poor response to circulatory stress In others, the superimposition of positive deleterious principles may serve to undermine the compensatory mechanisms which operate normally The precise role of each of these factors in different experimental syndromes must be determined in each instance

Selkurt Do you imply that the ability of the liver to inactivate is somewhat increased in the course of developed resistance; and if so, what role can you now ascribe to the kidney in terms of the opposing mechanism?

Zweifach Our *in vitro* data in resistant rats clearly indicate that the capacity of the liver to inactivate ferritin is greater than that of normal control rats Furthermore, the inactivation mechanisms do not become impaired following a degree of hypoxia which, in normal controls, is sufficient to destroy this capacity almost completely There remains the possibility that positive compensatory factors, such as arise in the kidney, contribute to the development of resistance In this regard it was found that rats, which had been made resistant to drum trauma, maintained this resistance after surgical exclusion of the kidneys One would therefore have to assume that the deficient compensatory response following nephrec-

tomy was adequately counterbalanced by the augmentation and protection of liver VDM inactivation mechanisms

Fine May I ask whether you have tested this effect on the mesentery by the use of bacterial products, say bacterial toxin?

Zweifach In 1943, we were stimulated by the results of Aub and co-workers (26) on the possible contribution of clostridia toxins to the development of irreversibility in shock We therefore set out to determine whether the shock produced by such bacterial toxins in normal dogs and cats resulted in the characteristic sequelae in the terminal vascular bed of the mesentery which we had observed following hemorrhage In these experiments, bacterial toxins (Clostridium welchii, Cl perfringens, Cl septicum and Shiga exotoxin) were injected in sufficient concentrations to produce a lethal effect three to five hours after intravenous administration The omentum was exteriorized so that the terminal vascular bed could be studied throughout the development of shock

For a period of several hours there were no changes, either in blood pressure or in the terminal vascular bed Then, toxic effects on the capillary wall began to appear, petechial hemorrhages developed, many capillaries and venules showed vascular stasis, gross evidence of edema was prominent in the gut These vascular phenomena were then accompanied by the development of vascular hyperreactivity, such as is evident following blood loss The blood pressure showed a progressive decline at this stage and within several hours reached profoundly hypotensive levels During the terminal phase of this type of shock, vascular hyporeactivity developed

Fremont-Smith But no fall in blood pressure in the early stage?

Zweifach There was no fall in blood pressure until capillary damage of the type described had appeared

Fine Did you, in the rat, with the mesentery exposed, try out the effect of bacterial toxins?

Zweifach In normal rat preparations, as used for the bioassay of vasoactive principles, the intravenous administration of clostridia toxins had no demonstrable effect on vascular reactivity for a period of one hour after intravenous administration The observations were not continued beyond that time

Fine Have you been able to prevent irreversibility by immunizing the animal to ferritin?

Zweifach It is impossible to immunize a dog against homologous dog ferritin

Fine Well, ferritin from some other animal I thought you were able to produce an antiferritin serum

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livers of Dibenamine-protected animals to see whether they are resistant to anoxia in a similar manner to that exhibited by trauma resistant rats

Nickerson In other words, this apparent resistance could be due to the fact that the liver is actually not as anoxic in the Dibenamine-treated animals?

Zweifach Yes, it is probable that Dibenamine serves to prevent the development of shock and to minimize the stagnant hypoxia within the tissues, rather than to protect against the deleterious effects of stagnant hypoxia on the liver after shock has developed

Shorr Could you rephrase that question?

Nickerson The basis of my question is whether the resistance of this system in Dibenamine-treated animals may not be due to the fact that the anoxia is less severe rather than to a direct effect of Dibenamine on the inactivation mechanism I think the distinction is very important from the standpoint of the mechanism of action of Dibenamine.

Zweifach Dibenamine-treated animals readily survive a standardized trauma or hemorrhage which consistently has a fatal outcome in controls The terminal vascular bed and the liver of such animals do not show evidence of decompensatory changes The precise mechanism responsible for the protective action of Dibenamine is as yet unknown

The Dibenamine experiments were done on both rats and dogs These animals were subjected to a standardized type of graded hemorrhage in which the blood pressure was arbitrarily kept at a moderate level of hypotension and then lowered to drastic hypotension (35 mm Hg, or below) The animals were maintained with infusions, if necessary, for a selected period of time and then were infused with the pool of blood which remained Normal controls, subjected to such procedures, show a high percentage of fatal shock Dibenamine-treated animals show few, if any, fatalities *

Haist This does not mean that these Dibenamine-treated animals are not more easily killed by exsanguination

Zweifach Animals treated with Dibenamine do not tolerate rapid withdrawal of blood In this respect they resemble sympathectomized animals

Fremont-Smith Have you studied the livers after Dibenamine?

Zweifach Preliminary *in vitro* studies on the livers of Dibenamine-treated dogs subjected to shock indicate that the hepatic VDM-inactivation mechanism, in contrast with control experiments, does

* Baez, S, Zweifach, B W, and Shorr, E Unpublished data

Zweifach One can obtain immunization with heterologous ferritin, such as horse spleen ferritin The question remains whether or not this type of immunization has an *in vivo* effect against the animal's own ferritin In any event, animals immunized with heterologous ferritin are not protected against the development of irreversible hemorrhagic shock

Nickerson Can you protect effectively with passive immunization?

Zweifach We have not produced sufficient amounts of antiferritin sera to attempt passive immunity experiments

Fine This antiserum, as I understand it, is an antiserum only for the ferritin of the animal

Zweifach Dr Mazur prepared samples of crystalline ferritin from horse, dog, rat, and human tissues These ferritin preparations were then injected into rabbits, and antisera, specific for each species, were obtained Such antisera will selectively affect homologous ferritin and, to a certain extent, heterologous ferritin in the test tube To what extent cross reactions occur *in vivo* has not been ascertained

Shorr The cross precipitation is strong enough to tie up the amount of ferritin we have present in the test tube

Moore Have you studied human blood from patients in varying stages of shock or collapse in your test animals to see if you could reproduce any parts of this nice sequence?

Zweifach Both VEM and VDM have been shown to appear in the blood of patients with different syndromes We have not had an opportunity to assay the blood of many patients in shock During World War II assays were done on several patients whom Dr A Cournand and Dr D Richards were studying In one of these patients, who later was found to be irreversible, we found VDM to be present in plasma, despite transfusion therapy In two others, we found VEM in the blood These observations are too fragmentary to permit us to make any statement concerning their validity

Moore I would not differentiate between their reversible and irreversible phases As far as the human is concerned, I just meant, have you discovered VEM? Have you ever found a patient in whom you could unmask the VDM by neutralizing the VEM?

Zweifach We have no fractionation data on the blood of patients in shock

Nickerson In connection with the resistance of the VDM-destroying system in the liver after Dibenamine treatment, was the system shown to be resistant to anoxia *in vitro*?

Zweifach We have not carried out *in vitro* experiments on the

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not deteriorate following three to four hours of drastic hypotension (30 to 35 mm. Hg)

Burch With titration for sensitivity to VEM and VDM, can a difference be found after Dibenamine?

Zweifach I cannot give a direct answer to this question The experimental findings differ with the dose of Dibenamine which is used and the time after Dibenamine administration. In shock experiments, the animals receive a given dose of Dibenamine the night before the experiment The following morning a typical blood pressure depressor response is obtained with intravenous epinephrine Omental studies on the reactivity of the metarterioles and precapillaries during the control period before hemorrhage reveal that the basal threshold reactivity to epinephrine is elevated In this respect, the Dibenamine-treated animal resembles the sympathectomized dog It is significant that the vessels in the terminal vascular bed respond to topical epinephrine despite the adrenolytic action of the drug as evidenced by the depressor effect of intravenous epinephrine on the blood pressure

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THE NERVOUS SYSTEM IN SHOCK

JOHN W REMINGTON
Department of Physiology
University of Georgia School of Medicine

AGAINST THE ADVICE of those who would not encourage a definition of shock, I begin boldly with the thesis that work on the shock problem has been hamstrung through lack of a definitive vocabulary by which various investigators could converse There have been many animals killed by a great variety of techniques, and each worker carries in his mind a picture, unexpressed in words, of the pattern of signs that preceded death There has been a constant stream of definitions of shock, none widely accepted, either because they were so vaguely termed as to be rather meaningless or because they did not frame the picture that someone else had And so we go blithely on talking about shock, whether we are working with dogs, cats, rats, guinea pigs, goats, or humans, as though it were always the same thing, but we are not really talking each other's language

It would be rather foolish to stir up the old argument whether or not the nervous factor is present in shock without trying somehow to define our terms more accurately I confess that we in Georgia have been quite guilty of evasion When we worked on acute, lethal hemorrhage, we very carefully did not label it shock, for that would have raised an angry voice of protest from the Western Reserve school of thought If, however, death was produced by muscle trauma, we felt safe in calling that shock simply because we had used one of the so-called shock-producing procedures If, in the course of an experiment not connected with the shock problem, an animal failed on the table, that was called deterioration However, the more dogs I see die, the less convinced I am that there is any major difference

Perhaps we should forget that the term "shock" was ever coined and admit only that we are students of the death process I have seen six general patterns in this death process Two of them can be discarded as not immediately pertinent, both are acute and, fortunately, relatively rare One of these two is a presumably cerebral death, with failure of respiration while the circulation is still fairly adequate, as is seen after too large a dose of anesthesia The

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the dog, we have usually bled slowly and stepwise During the bleeding process, the arterial pressure is first sustained through cardioacceleration and through a moderate rise in resistance At the end of the hemorrhage, the arterial pressure is reduced to, say, 40 mm Hg At this time the heart rate is over 200 per minute, and the flow has been lowered to values between 1 and 1 5 L.

Moore How is that measurement made?

Remington By dye injection, by direct Fick, or by pulse contour. They all give the same answer

Howarth Are these anesthetized dogs?

Remington. Yes, enough so that I can put sounds in to record their pressures and place a catheter into the heart.

Howarth What is the anesthesia?

Remington Our usual regime is to use a rather heavy morphine sedation followed by a small amount of sodium pentobarbital, just to allow the neck surgery The dose is not over 15 mg per kg After the surgery, time is allowed for the dog to quiet down if that is necessary After an hour or so the animal cannot be said to be under anesthesia, but rather it is in a more or less hypnotic state, lying quietly unless stimulated

Green Do you continue the morphine or give just one dose?

Remington Just one dose

Stead What about the arterial oxygen tension and CO_2 content?

Remington They are fairly normal Of course, most of our Georgia dogs, coming off the street, are on the anemic side The arterial oxygen under the regime is about 18 or 19 vols per cent

Stead I did not mean oxygen content I meant tension

Remington You mean, how fully saturated they are?

Stead Yes

Remington They are somewhere between 90 and 95 per cent saturated, uncorrected for dissolved oxygen There is no obvious distress of respiration, and, while oxygen consumption is down somewhat, it is fairly consistent from animal to animal Arterial blood total CO_2 is generally from 40 to 50 vols per cent

Fine Have they fever?

Remington No

To return to our type one pattern, the resistance, starting off at 2 (Pm-20/flow per sec per M^2)*, may, at the end of the hemorrhage period, have increased to 2 2 or 2 3 or may remain unchanged As a scale of comparison, if one injects epinephrine into an animal to raise its pressure from 100 to 140 mm Hg, the resistance will rise from

* EDITOR'S NOTE Pm is an abbreviation for mean arterial pressure in mm Hg

other is acute heart failure, with dropped ventricular beats, leading usually to fibrillation. However, most dogs die, no matter what the lethal insult has been, after a gradual fall in arterial pressure and in cardiac output over the course of several hours

MAJOR PATTERNS OF SHOCK

Four major subdivisions of this pattern can be described Type one is the most common in the laboratory, and it can be reproduced easily by simple hemorrhage The arterial pressure and flow (i e, cardiac output) decline proportionately with but little change in calculated resistance (Figure 7)

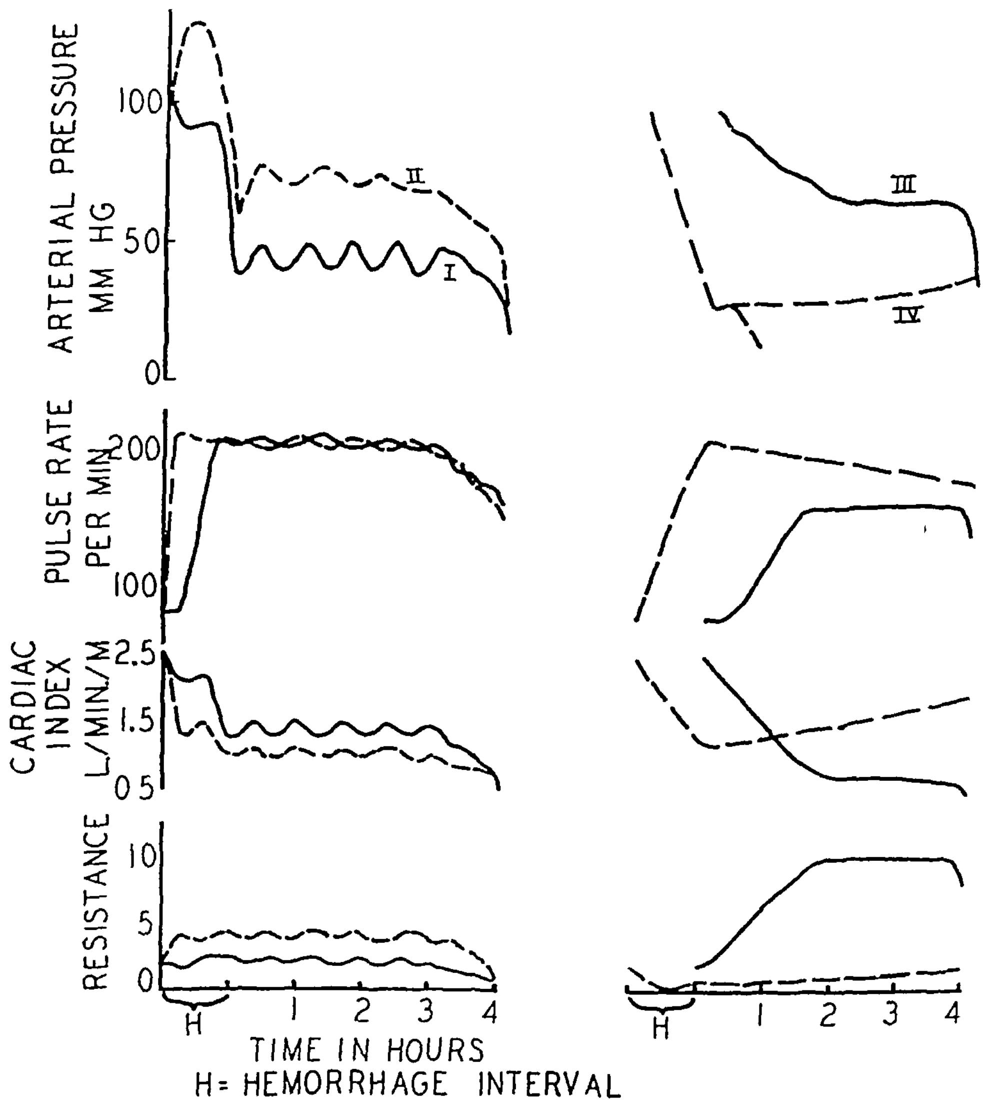


FIGURE 7 Major patterns of shock

I am not sure it makes a great deal of difference how the bleeding is done Being interested in the sequence of vascular reactions in

Using an animal subjected to hind leg trauma as a prototype, with the start of the trauma, the pressure and heart rate immediately rise The respiration becomes quite fast The animal may come out of the anesthetic, so that more pentobarbital must be given In this pressor phase, the flow is curtailed As trauma is continued and as fluid is lost into the legs, the pressure falls to about 70 mm Hg After the trauma is stopped, the pressure climbs somewhat and then fluctuates about the higher level

After several hours, just as in type one, the dog suddenly quiets down, respiration is depressed, and the pressure falls very rapidly to death Heart rates are quite similar to those of type one The cardiac index falls during the trauma to around 1 L. per min , and shows but little subsequent rise after trauma is stopped Again the fluctuations tend to be reciprocal to resistance changes

Resistance, with the start of the trauma, rises significantly to values of from 3 to 4 This rise is comparable to that seen after a small dose of epinephrine The resistance remains well above normal until the final slump That afferent impulses have influenced the immediate reaction to trauma cannot be denied It also seems that the continually elevated resistance reflects neurogenic factors

In other words, the major differences between a type one and type two response are the higher pressure values held, the tendency toward lower flow values, increased resistances, and less blood loss

Fine How much less blood loss and how do you measure that loss? Is that blood volume?

Remington We know that to produce a fatal type one reaction requires the removal of from 35 to 50 ml per kg of blood We have not directly measured the blood loss in the dog subjected to hind leg trauma The fluid loss reported in other laboratories (1), after the same procedure, is of the order of 25 to 30 ml per kg

Moore Those lower figures are based on limb weights, aren't they?

Remington Some of them are

Green Wouldn't that be about the plasma loss from the bleeding?

Remington No, because if all loss into the leg was plasma, the hematocrit should be very high indeed in these dogs Actually, the hematocrit may increase from a control value of, say, 40 per cent to 50 per cent In most cases the rise is much less

Green You must have hemorrhage in the leg as well?

Remington Yes If one cuts the skin of the swollen leg, blood-tinged fluid comes out

Bradley Is the calculated vascular resistance corrected for this

2 to about 4 or 5 so that this posthemorrhage rise is not very great.

After hemorrhage is completed, circulatory values remain about as they were, but periodic variations are evident The dog is actively fighting to restore circulatory function I do not know how to describe what I mean by "fighting," but I think you have all seen it. He has active reflexes, his respiration tends to be more rapid than before the bleeding, oxygen consumption is normal, or depressed moderately, the blood pressure is never stable, varying from, say, 30 to 50 mm Hg. The heart rate also is not stable. It usually will not fall below 200 in its excursions Flow is still severely depressed, fluctuating between a liter and a liter and a half Resistance changes tend to be reciprocal to flow

And then suddenly something happens to this dog He quiets down If he has been practically out of the stuporous condition, he relaxes Blood pressure and flow fall slowly, but uninterruptedly, and he eases out to death In this latter phase, the heart rate settles down to a stable rate, usually somewhere below 200 The flow is reduced to about 0 8 liters within about fifteen minutes before death, and resistance at this time is decreasing markedly

Moore. Do you have serial hematocrits to show how fast he is hemodiluting himself?

Remington As far as the dog is concerned, dilution of the blood is seldom as much as 10 per cent

Moore In four hours?

Remington In four hours And very often there will be no dilution whatsoever What dilution has been accomplished does not start with the hemorrhage, but rather late in the bleeding period, just before the abrupt fall in blood pressure The dilution often ceases as the pressure reaches low levels Hence, the compensation, if you want to call it that, by which the animal attempts to raise its pressure is not dependent in large degree upon the ability to imbibe fluid from the interstitial spaces, and thereby increase the blood volume

Stead Does it make any difference if his spleen is out?

Remington As for hemodilution, no As for other consequences of splenectomy, the animal shows the pattern we shall call type two

The type two pattern is seen in an animal that has been subjected to trauma, be it contusion of the hind leg, or entry into the abdominal cavity to tie off the spleen or kidneys or for more extensive surgery It may also be seen in a dummy operation consisting of abdominal entrance and immediate closure The duration of the posttrauma pattern may reflect, of course, the duration and extent of the trauma

Remington: Normals vary a good deal. Normals, we will say, are anywhere from +2 to +5 mm Hg. With the initial hemorrhage, before the heart accelerates, that may drop by a millimeter or so. In other words, there will be a range of +2 to +4 mm Hg. The animal with +2 may not show any change. The animal with +5 will usually show some drop.

Green: To what point do you refer your zero pressure?

Remington: Zero is usually referred to the apex beat.

Selkurt: Is that a net pressure, corrected for the intrathoracic pressure?

Remington: In most cases, these are not so corrected. As the heart accelerates, venous pressure always falls because of the increased inflow into the heart. After the acceleration, pressures usually lie between 0 and +2 mm Hg. This level is then held until the animal shows the late pressure and resistance fall, when, in some cases, it may again rise.

Burch: What about at death and after he is dead?

Remington: After he dies, it is high.

Burch: How high, though?

Remington: I don't know.

Burch: How about the arterial pressure after he dies?

Remington: I have not attempted to find out, and any such readings would be accidental rather than intentional. I think the pressure is around 10 mm Hg or so, but that may be too high.

Burch: Are the arterial and venous pressures the same in the dead dog?

Remington: I really don't know. I assume that they are, but I don't know.

Burch: After the heart stops beating but when he is still warm and rigor mortis has not been established, are the pressures equal?

Sharpey-Schafer: They are in a dead man, surely.

Burch: Yes, they are in a dead man. I was speaking of a dog dying with hemorrhage shock and without much blood to distend the vessel.

Fremont-Smith: Death is a sort of gradual process, so you have to say how dead. I think the pressure would do the same thing if he were dead enough.

Burch: If the blood volume is low, the continuity of the vascular lumina may be interrupted.

Nickerson: The valves would not be completely patent.

Remington: Turning to type three, it is a pattern I have seen very much recently, but because it is recent, I really know least about it.

constant change?

Remington: No.

Fine Can you assume that that amount of bleeding, 25 to 30 per cent, represents whole blood loss? There may be differences from the normal proportion of red cells to plasma in the extravasated fluid

Moore: It is not being maintained that they are the same It is not germane to the argument

Fine. I think it is germane with respect to what is happening to the hematocrit.

Remington. If one of these type two dogs has been given Dibenamine, prophylactically, he does not show the elevated resistance, and his flow does not fall as far. For the same amount of trauma, the flow will fall to around 1 5 to 2 L per min. Such flow levels in a posthemorrhage animal are not critical Nor is the Dibenamine-treated, traumatized dog in any critical danger. He promptly recovers He still shows the same hematocrit change as the untreated control, and, as far as we can tell, the legs swell as much

Shorr When do you give the Dibenamine?

Remington· The Dibenamine is always given before the trauma is started

Burton Does his pressure go lower after the Dibenamine?

Remington. His pressure drops during the trauma and reaches lower levels than in the control

Nelson. What does the blood pressure do in the Dibenamine-pretreated animal with the initial blow to the leg?

Remington The initial response depends on the dosage of Dibenamine used With a large dose, the pressure falls at the beginning With a small dose, which does not produce as much epinephrine reversal, the pressure may climb at the start of trauma, just as in the control, but then it falls faster and to lower levels

Fremont-Smith What about venous pressure?

Remington If we mean as venous pressure the filling pressure of the ventricle, the venous pressure in type one may drop off slightly in the early hemorrhage, or it may not As the heart accelerates, venous pressure always takes a sharp drop

Burch Is the pressure the intraventricular pressure or pressure in a vein?

Remington The pressure is taken either from late diastole in the right ventricle or from the crest of the auricular wave in the auricle

Burch What is the level of pressure? Could you give us values?

Fremont-Smith What would be the normal?

toneal cavity does not gain much water

Stead Does the sodium chloride pass into the water in the belly?

Remington Yes No matter how we produce this pattern, the dog's pressure during this blood volume reduction may stay the same or it may fall to 70 to 80 mm Hg The heart rate accelerates gradually, but seldom to a value above 200 per minute Usually it is from 170 to 200 per minute One cannot place this pattern on the same diagram, for there is no discrete hemorrhage period Blood volume loss (hemoglobin increase) is more or less steady over the four-hour period If anything, the loss is more rapid in the later hours

Fine How much isotonic glucose has been given into the peritoneal cavity?

Remington We have given either 100 or 150 ml per kg

Moore So you have been putting 1500 ml of 5 per cent glucose into a ten kilogram dog

Fine That is enough to produce water loss, fall in blood pressure, compression of veins, and so on?

Remington Yes

Fine And he loses blood volume?

Remington· Yes

Moore As established by what technique?

Remington By increase in hemoglobin content of the blood

Hyman Have you any idea of the intra-abdominal pressure of these animals?

Remington It varies, depending upon the build of the dog and the amount of glucose injected We have not been able to support the idea that death is produced by an elevated intra-abdominal pressure I have given dogs 200 ml per kg of isotonic salt solution without critical consequences I have blown the abdomen up with air to a pressure of 120 mm Hg, and put the dog back in the cage, it still had a swollen abdomen the next day but was active and ate well

Stead Did the hematocrit and protein go up together in your glucose preparation?

Remington Quantitatively, yes

Hyman We did some pressure breathing in cats and were able to move water out into the exposed portion of the beast regularly and easily although the pressures employed were considerably less than 120 mm Hg (2)

Remington To return to a description of type three, flow in these dogs falls steadily and to the extremely low levels of from 0 5 to

It is seen in death following partial occlusion of a large vein. It is also seen in a dog that has been given an interperitoneal injection of isotonic glucose solution I do not want to go into the details of the method, or the reasons behind choice of that particular technique But, in essence, the procedure lowers the blood electrolyte levels quite acutely, and reduces blood water, too As far as we can tell, the reduction in blood volume, as measured indirectly from hemoglobin change (splenectomized dogs), is of the order of about 10 per cent, which, assuming an initial blood volume of 95 ml per kg , represents a blood volume loss of the order of 10 ml per kg The fluid loss is, of course, plasma

Moore I beg to differ It is not plasma It is extracellular fluid.

Remington I am not sure that I will accept that completely I can find all the proteins The red cells should be gaining water under these conditions

Moore. You mean each erythrocyte has more water in it?

Remington: Yes

Moore Not much It may have a little more

Remington I know I can't find it either, but the red cells have gained water.

Moore Why?

Remington Because the blood sodium and chloride have been reduced

Moore How much?

Remington Sodium from 110 to 150 down to 100

Moore That is not necessarily going to change the total osmotic pressure It may make the red cells a little rounder, but it won't account for a 10 per cent volume change

Remington But at least they are not going to lose water

Moore I will accept that

Remington And the plasma has

Moore That is right And all that water has not come from the plasma That is what I was saying

Burch The extracellular fluid must have decreased to some extent, don't you think so, Dr Remington?

Remington Surely I am not measuring extracellular fluid I am interested in the blood

Fremont-Smith What he is saying is that as the water is taken out of the plasma into the peritoneal cavity, the blood picks up extracellular fluid from other parts of the body

Remington Not in the dog It doesn't go into the peritoneal cavity I don't understand that, but it is not like the rat The peri-

Nickerson. We have used the intraperitoneal glucose procedure to change electrolyte balance for other reasons, and within the period of these experiments, four hours or so, we have found absolutely no difference in the results whether the solution was left in or removed after an hour or two. You can remove almost the total volume that was put in. The difference appears after about twelve hours. With sublethal amounts of glucose solution, the animals with the solution still in the abdominal cavity recover, whereas the animals from whom the electrolytes, plus glucose and water, were removed continue to go downhill and may or may not recover.

Moore. Have you analyzed the fluid taken out?

Remington. Yes.

Moore. You have removed about half of the dog's extracellular potassium, haven't you?

Remington. I have not analyzed for potassium. I have simply relied on the results in the literature. After all, this technique has been worked on for fifteen years. While some reports indicate an elevation in plasma potassium, and others a fall, the change is seldom more than 1 or 2 mEq. (3,4,5). This change hardly seems sufficient to account for the fatal circulatory changes.

Moore. My only point was that after you leave the glucose in and then take it out again, you are not just taking out glucose. You are taking out everything.

Remington. Everything that has entered the peritoneal cavity.

Nickerson. After an hour or so, the intraperitoneal fluid has essentially the same electrolyte content as the plasma.

Green. What happens to venous pressure during this terminal phase?

Remington. I can't answer that. I have venous pressure records but I have not codified the data. Central venous pressure tends to be low, however.

Stead. What about beforehand? Is the venous pressure normal through that first part of the observation?

Remington. No. Starting with a slow-heart dog, the initial venous pressure is moderately high. With acceleration, the pressure falls. Whether there is a disproportionate drop at any time during the syndrome, I cannot, at present, answer.

Bradley. In humans with increased intra-abdominal pressure of only 20 mm., the cardiac output appears to fall by as much as 20 per cent in some individuals. The blood pressure does not change. Hence, one may assume that the resistance has risen.

Howarth. From observations Sherlock and I made on cases of

1 L. per min That is well below the lethal level in a bled animal It is rather comparable to the cardiac index seen just before death in either of the two previous types of animals Yet this dog exists with these flow levels for several hours. He is a vegetable, without reflexes, needing no anesthesia. There are no fluctuations in pressure or flow

Burch· How much time is required for that syndrome to develop?

Remington: That varies The pattern may develop fully within the course of an hour With the very low cardiac index and the relatively high pressure, the resistance is very high and stays high Finally, without any warning, there is a sudden fall in pressure and resistance, and the animal dies The basis for the high resistance is not clear. There is no obvious locus for afferent stimulation, such as there was after trauma If I give one of these animals Dibenamine, at least the major part of the resistance rise is canceled, but the flow may not be greatly improved and the dog is doomed Life can be saved early in the sequence by intravenous injection of a large amount of hypertonic salt solution. Later on, this is not effective

Green Do resistance and inflow drop off when the pressure drops off?

Remington: Yes

Stead Have you ever measured the terminal pressure in the dog's system after death?

Remington No

Burch. How about hypertonic sodium chloride?

Remington The intraperitoneal injection of a hypertonic solution gives marked nervous stimulation, with very rapid respiration and twitching movements Later, as plasma volume is reduced, and hematocrit and hemoglobin rise so that calculated blood volume loss is around 30 per cent of the initial volume, the dog fails The general response is that of type two

Shorr What happens if you relieve the intra-abdominal pressure by removing the isotonic glucose?

Remington Nothing In one dog, for example, I tried to keep a constant infusion of isotonic glucose through the abdominal cavity without allowing, at any one time, a large volume of intra-abdominal pressure The dog showed the full syndrome

Shorr If, at the end of an hour after the new hemodynamic situation has developed, you relieve the intra-abdominal pressure, does anything happen?

Remington. I have not tried it, but I would doubt it very much

vagus. I have never encountered other than a pressor response. This reaction can be seen in animals given a large dose of Dibenamine. If such a treated animal is bled, the pressure falls very rapidly to levels to 20 to 30 mm Hg. It is obvious that if more blood is taken, death will follow abruptly. If bleeding is stopped, even though the total amount is small, the dog shows low pressure and flow values for several hours and then, very slowly, both values start rising. Heart rate may remain fast or may decelerate somewhat.

Fine: What is the average blood loss?

Remington. The loss is from 15 to 20 ml per kg. In these animals, the critical value seems to be not arterial pressure but flow. If the cardiac index is reduced below about 1 L per min, the animal will die. If not, it can spontaneously recover. In this process, the dog is a vegetable, too, until suddenly he is out of the anesthesia. His pressure may still be low when this happens.

This type has been presented because it may have some counterpart in what I have been told is a clinical pattern. Very often after cyclopropane anesthesia, and after abdominal surgery, especially where the surgery is extensive and involves traction, there may be a pressure fall that resembles a syncope type of reaction, but in which the skin turns cold and the pressure may not rise spontaneously. The heart may remain slow throughout. Sometimes after several hours of hypotension, the heart rate may accelerate, or the slow rate may be maintained to death. That appears to be a predominately depressor neurogenic response.

Fine: You say that occurs in man?

Remington: Yes.

Moore: That is rare, don't you agree?

Fine: Yes. I am trying to think of an illustration.

Moore: And under cyclopropane it is so hard to do anything in the abdomen.

Bradley: In cyclopropane shock the skin stays warm.

Remington: That is the syncope type of hypotension where the cardiac output is elevated. I am talking of a sudden fall in pressure, a slow heart, progressively cooling skin, and loss of consciousness. These individuals have lost blood.

Sharpey-Schafer: In anesthetized or unanesthetized?

Remington: Postoperative, and perhaps in other states.

Sharpey-Schafer: I think there is quite a difference.

Bradley: This kind of thing is common on awakening from cyclopropane anesthesia, but I have never seen a patient die from it.

Moore: I have seen this response under very deep anesthesia,

ascites of varied etiology, it would appear that intra-abdominal pressure can be varied over a wide range by tapping or further distending the abdomen without producing significant changes in cardiac output A considerable rise in intra-abdominal pressure seems to be necessary before a rise in venous pressure occurs.

Bradley. That is true of venous pressure in the upper part of the body but not in the area caudal to the heart

Howarth. These measurements of venous pressure were made by cardiac catheterization in the unanesthetized human subject in the supine position.

Moore And measuring venous pressure where?

Howarth: In the right auricle

Bradley I agree with you. The auricular pressure may not change at all

Moore The venous pressure in the leg would go high.

Bradley Exactly

Moore What happens if you give the dog that same huge amount of 5 per cent glucose intravenously, rapidly, so that you are not even putting a membrane between that and the extracellular fluid?

Remington I have not tried that experiment

There is one other thing that helps us diagnose this type three, a rather unique type of pulse contour On this basis, there is a suspicion that some of the posttransfusion hemorrhage dogs are also on the borderline of this type three response As I said, I know least about type three, and I have entered it here simply for completeness.

Type four may have some counterpart in the human, and it also has neurogenic factors The dog starts off with a syncope type of reaction, with a primary fall in resistance, the pressure falling low and the flow remaining relatively high If the animal showing the syncope reaction has suffered hemorrhage, however, the flow may fall and death may ensue

Now, I confess complete failure to produce a syncope in a normal dog In my search I have tried various types of trauma, including stretching of mesenteries, manipulation of the celiac plexus, traction on the viscera, the breaking of bones, and manipulation of the ends of the broken bones

Howarth Have you tried it in the dogs without any anesthesia at all?

Remington I have not seen syncope in morphinized dogs

Howarth Have you ever observed a sudden onset of bradycardia without any change in blood pressure?

Remington: No, except, of course, by a direct stimulation of the

Remington I presume that the veins will also be large

Burch Of course, every vessel cannot be dilated What veins do you mean? Do you mean the veins of the organ?

Remington The distal veins, or perhaps only the venules

An untreated dog, by constriction, can return blood from the tissues back into the central veins and replenish that central reservoir If a dog is given a large dose of Dibenamine, the blood removed in a hemorrhage must come in greatest part from the reserve volume When reserve blood can no longer ensure a high flow, the animal is in trouble Through failure of constriction, the lethal bleeding volume has been very severely reduced If, after Dibenamine, bleeding is stopped when the reserve blood volume is depleted, this dog can recover Of course, this dog has a greater blood volume than would a control from which more blood had to be taken to produce the same pressure fall But the Dibenamine-treated dog also has a larger peripheral bed capacity, and what is important is blood volume level only as related to the size of that vascular tree being circulated

On the other hand, what are the penalizing effects of an intense vasoconstriction? I am using the term guardedly, because all I know is that a nerve stimulation gives rise to the high resistance of the type two dog If the resistance rise is prevented, the dog can recover from a traumatic procedure which ordinarily would be lethal Why this should be, I don't know There have been many studies on flows through isolated organs As you all know, during the period of active compensation after bleeding, when the general resistance does show the small rise, the leg flow, for example, decreases to an immeasurable amount, and it is never restored

I will not stand behind the thesis that a heparinized dog with a rotameter in place is comparable in all respects to the intact dog Furthermore, I am very much disturbed about the attempted addition of separately recorded flow rates through the various body circuits If we accept evidence from this type of preparation, however, it would appear that some beds show this intensive constriction, and also, since there is no really great rise in general resistance, that some circuits in the body are either not showing resistance rise or are actually dilating In the latter category, one would immediately think of the circulation to the brain and the heart Quantitatively, however, the flows in these two beds do not seem to add up to enough If, during hemorrhage, there is an intense constriction in some regions and a shunting of blood into organs where flow is not so curtailed, why does the animal die when he still has half

but I have never seen it go on to fatality.

Haist Regarding the sudden fall in blood pressure, slow heart, and cooling skin, may I offer a comment concerning the rat shocked by a clamping procedure? When clamps are released in rats which have had the clamps applied for twelve hours or so, there is a fall in blood pressure, a reduction in heart rate, and a fall in skin temperature and rectal temperature, which is rather abrupt in some instances.

Remington. Clamps placed where?

Haist On both hind limbs The clamps were broad, covering much of the thigh and were left in position for a period of twelve to fourteen hours, and then removed

Remington. This response is certainly not typical of the picture following tourniquet release in a dog

Haist This was obtained in the unanesthetized rat after a clamping period of twelve to fourteen hours, which is a long clamping period

Shorr. Do you think, Dr Haist, this might be due to the release of adenylic acid?

Haist I don't know Some of these changes can be altered by reclamping The interesting feature was the fall in heart rate. The greatest change was in the early period following the release of the clamps, subsequently, it fell more slowly.

Remington Why should vasodilation reduce the lethal bleeding volume? If we start with quiet dogs with slow hearts and fairly minimal cardiac indexes, the heart is big, the veins are well filled, the venous pressure tends to be moderately high We can say that such a dog has a fairly large volume of reserve blood I am not going to define the term "reserve blood" Some of it is residual blood in the heart; some of it occupies the pulmonary circuit and large veins If that dog is given a vasodilator, the bed distal to the arterioles opens up, and blood goes in to fill that bed That blood has come from the arterial system and produces a pressure fall

Nickerson You are speaking of a dilatation of the arterioles, are you not?

Remington Arterioles I know nothing about what is beyond I will let others tell us about the capillaries

Burch Might they be dilated also?

Remington Presumably they are, passively or actively But certainly the whole organ will gain volume, so that the whole, or part, of the distal bed is being filled with blood

Sharpey-Schafer What about the veins?

traumatic or hemorrhagic shock, we exposed the animals to an equivalent degree of hypotension or to an equivalent degree of trauma We have not attempted to expose animals to a greater amount of trauma

Remington What seems to be confusing is that the results depend upon the dosage level of Dibenamine If a large amount is used to give relatively complete epinephrine reversal so that, when the animal tries to compensate, his pressure always falls and cannot be spontaneously raised, then the amount of blood that I take out in single or progressive bleeding is definitely less

Stead You can make him more sensitive to bleeding and you can kill him more quickly What about trauma?

Remington Unless bleeding is stopped when the pressure is very low, the dog will die acutely

Moore You made the statement a moment ago that Dibenamine reduces the lethal bleeding volume Then, by extension, it makes him more resistant to the traumatic loss

Remington All right

Stead I am still not clear In absolute terms, can a dog, after the Dibenamine, stand more trauma than the normal dog and live?

Remington As for muscle trauma, with a large dose of Dibenamine, the dog will die during the course of trauma With a small dose of Dibenamine, so that the dog can constrict some, the dog can be traumatized as much as can the control, the cardiac output does not go to dangerously low levels, and the animal recovers

Stead So that there is a difference between the actual blood loss?

Remington If we use a small amount of Dibenamine, so that it is still possible for the animal to constrict but not to a normal degree, then a full bleeding volume must be removed from that dog to reduce its pressure Once the pressure is down, the animal will turn right around and the pressure will slowly rise In other words, after Dibenamine, regardless of the dosage used, the animal can withstand low pressure values and recover from them

Burch But the amount of blood in his body is actually larger?

Remington Not with small doses of Dibenamine, his blood volume is no more

Burch You have bled the same amount from the dog to reach that lower level?

Remington Yes

Stead And you have measured the amount of hemodilution? There is no difference there?

Remington There is no difference there

his blood volume left?

Zweifach The figures on maximal blood loss which you have presented refer to the acute removal of large amounts of blood. We have found in shock experiments on dogs treated with Dibenamine that it is possible, through the use of graded bleedings, to remove as much blood from these animals as one would obtain from normal dogs. In other words, the maximal blood loss tolerated by Dibenamine-treated animals was within the same range as that of our normal controls, about 5.3 to 5.8 per cent of body weight. However, the control group of dogs was found to be irreversible to blood replacement, while 90 per cent of the Dibenamine-treated animals recovered. For these experiments different doses of a Dibenamine derivative, 688A, were used. In the dog, 2 mg per kg of body weight, given the night before the experiment, protected against the lethal outcome of hemorrhagic shock. This dose gave a definite blood pressure reversal (20 to 25 mm Hg) upon intravenous injection of 2 to 3 gamma of epinephrine. In the rat, from 5 to 20 gamma per 100 gm body weight was equally effective.

Remington How long do you wait between your bleedings?

Zweifach The precise interval between bleedings varies from animal to animal. In the procedure employed, the experiment is arbitrarily begun by bleeding 2 per cent of body weight. Successive bleedings are carried out, 1 per cent, 0.5 per cent, etc., with a wait each time until the blood pressure and the blood flow through the omentum have become stabilized. Immediately following each bleeding, the blood flow through the omentum is temporarily curtailed. Dibenamine-treated animals can be bled, despite pressures as low as 40 or 35 mm Hg, without precipitating circulatory collapse.

Stead Is the hemodilution in those dogs the same as in the control, Dr. Zweifach?

Zweifach We have no data on the relative hemodilution in these experiments.

Stead That might make a difference.

Zweifach The feature which impressed me most was the maintenance of an adequate circulation through the omentum, despite the fact that the blood pressure had fallen to levels as low as 30 mm Hg.

Stead As I understand it, in your hands, the dog, after Dibenamine, is much more sensitive to hemorrhage. You can kill him more easily by bleeding, but he will withstand a greater amount of trauma.

Shorr In our experiments on the influence of Dibenamine on

Remington My concept of homeostasis is slightly different for the dog In the dog, epinephrine primarily gives vasoconstriction As the dog prepares for flight, constriction takes place to raise his pressure When the muscles or organs go into activity, the arterioles to the bed in question are opened and the high pressure produces a vigorous flush through those beds If the dilated bed is too extensive, constriction of inactive beds will maintain the pressure and increase the reserve blood volume Progressive bleeding will ultimately evoke the same pattern of constriction in less active structures, dilatation in the active ones But, ultimately, in the constriction, the flow through some vital beds must be penalized

Shorr Could you go further, Dr Remington, and tell us which beds are preferentially flushed, and why?

Remington I do not know As I said, there have been measures on flow, for what they may mean We have made attempts at measuring visceral flow, but I think our technology is not adequate for the job What we were getting was a combination of rotameter, or venous occlusion shock, and the response to hemorrhage. Taking the evidence for what it seems, it would appear that the viscera did not show constriction of the same order as seen in the hind leg

Zweifach· To Dr Remington's data we can add observations on the omental circulation and on the appearance of humoral factors Emphasis has been placed on the inability of the Dibenamine-treated animal to tolerate acute hemorrhage and this has been ascribed to an impairment of the vasoconstrictor mechanisms in such animals I should like to bring to your attention the fact that the arteries and veins possess an intrinsic tone which permits them to undergo progressive narrowing even after sympathetic denervation It is obvious that both the Dibenamine-treated and the sympathectomized animals have lost the capacity to effect a rapid constriction of their large blood vessels when blood is withdrawn However, when blood is removed slowly, these vessels were found to undergo progressive narrowing These observations again bring to the forefront the fact that the functional response of blood vessels is a composite of many factors

An interesting phenomenon is the failure of Dibenamine to prevent the usual sequence of vascular changes in the terminal vascular bed of the omentum The vessels undergo essentially the same type of hyperreactivity which is seen in normal controls Dibenamine, apparently, does not interfere with the mechanisms which regulate the blood flow in the terminal vascular bed

A further point of considerable interest is the fact that the venous

Green. I am a little confused between your control experiments and your experimental standards. You are taking one set of animals and bleeding them, another set of Dibenamine-treated animals and bleeding them, and comparing the results of those two groups?

Remington. That is right.

Green. What criterion is similar in the two groups of dogs? Are you bleeding them down to the same amount?

Remington. Bleeding them down to the same pressure.

Green. The Dibenamine-treated animal has a higher cardiac output at that same pressure?

Remington. No.

Moore. He has a higher blood volume.

Remington. Only with a large dose of Dibenamine, not with a small dose of the drug.

Nickerson. One point in our thinking about the sympathetic nervous system bears directly on the interpretation of these results with Dibenamine. We have always looked upon the body's vasoconstrictor mechanisms as being developed for the purpose of maintaining homeostasis. We may assume that in the evolutionary selection of this mechanism, homeostasis, to the animal which was attacked and perhaps was injured and bleeding, was largely a matter of maintaining an adequate blood flow through skeletal muscle. There seems to be very little basis for expecting that natural selection would evolve mechanisms directed at preventing irreversible shock. If the animal was down to the borderline between reversible and irreversible shock, his enemies would probably get him irrespective of how his sympathetics worked. So it is quite probable that from the standpoint of the irreversibility of shock, sympathetic vasoconstriction has evolved into a mechanism which diverts blood in the wrong direction in the shocked animal. Certain tissues, perhaps the liver with the production of VDM, which are involved in this irreversible process may actually be preferentially deprived of blood. The normal sympathetic homeostatic mechanism may be detrimental when we reach this borderline of the reversibility or irreversibility of shock. Irrespective of how you interpret differences in the actual amount of blood that is removed from the animal to produce a given level of hypotension, I believe that all of the results, with large or small doses of Dibenamine, can be fitted into the same interpretation. It is a matter of preventing some localized or generalized vasoconstriction which may have been advantageous to the wild animal but is detrimental to the animal faced with the fine distinction between reversible and irreversible shock.

thought that the veins would constrict after hemorrhage Instead, these veins dilate It may be that this is the reflex that Dibenamine knocks out, so that in the Dibenamine-treated animal, the veins do not reflexly lose their tone after hemorrhage

Fremont-Smith It might operate only under anesthesia

Burton There is some criticism Those of us interested in hemodynamics would have liked to know the venous pressure at the other end as well as the head of pressure But when you figure it out, the change in venous pressure could not possibly have accounted for more than a small part of the observed increase of the flow Even if the vena cava pressure fell to zero, it still could not have increased the total head of pressure very much and certainly could not have accounted for a two- or three-fold increase in drip rate

Moore Why does the increased drip rate make you feel that the veins have dilated? That interests me

Burton The total resistance to flow from the bottle right into the animal has decreased to about a third of what it was

Moore Wouldn't that be found if there were just an increased cardiac output? This needle is inserted into a major vein

Burton By the word "dilated," I do not mean to convey an active dilatation necessarily I simply mean that the channel has gotten bigger The resistance has gone down

Burch What you mean is that the pressure has dropped

Burton What I really mean is that the resistance to flow has gone down so that, with a given head of pressure, you now get much more flow That would mean there must be a wider bed

Burch I am not sure that is correct

Burton The vein must be bigger than it used to be I think you can't escape that

Burch Actually, the vein may fit less tightly on the blood that it is enclosing The volume of the vascular bed and the volume of the blood within it are always the same under all the conditions we are discussing This is always true in the closed circulation The only difference may be the tightness with which the "sleeve" or vein fits around the blood within

Moore And how many sleeves are open?

Burch Regardless of whether or not they are open, the volume within the vessel is equal to the volume of the lumen of the vessel

Moore Of course

Burton I cannot follow that What is in-between if the sleeve does not fit tightly? Is there a vacuum?

circulation in the omentum of the Dibenamine-treated dog has very little blood in it relative to the arterial circulation In normal controls, subjected to drastic hypotension, there is a gradual sequestration of blood from the arterial system in the terminal part of the capillary bed and in the collecting venules where it stagnates The blood returns to the large veins very slowly In direct contrast, the venules of Dibenamine-treated dogs, subjected to shock, show a continuous unidirectional flow of blood into the large veins Most of the blood which is in active circulation is on the arterial side of the system

Shorr The capillary compensatory reactions are well manifested

Zweifach The compensatory reactions of the terminal vascular bed to blood loss are essentially normal in dogs receiving 2 mg 688A per kg body weight

Burton I wish to mention some experiments, done in the last two years by Dr John Coles (6) under Dr McLachlin at Western, on the possible effects of venomotor tone in hemorrhage shock in dogs The results are extraordinary The work was done on dogs and rabbits anesthetized with Nembutal, with ether, or with chloroform, on unanesthetized dogs and on anesthetized and unanesthetized patients It includes investigations of the role of stimulation on the sympathetic, of afferent nerves and of the carotid sinus, with the effects of adrenalin and of Etamon HCl The standard level of the reservoir supplying the perfusion into the peripheral vein (usually the short or long saphenous) was 18 inches above the heart level, giving a pressure head of 34 mm Hg The findings were

a) The response to blood loss of as little as 1 per cent of body weight, or of 500 ml in humans, was relaxation of the veins concerned In unanesthetized animals or patients there is an initial venospasm preceding this, but not in trained animals or subjects The relaxation may precede the fall of blood pressure Reinfusion was associated with an increase in venous tone Intra-arterial transfusion was more effective than intravenous

b) Sympathectomy on one side delayed the relaxation on the denervated side

c) Adrenalin, stimulation of the sympathetic chain (in humans), stimulation of afferent nerves, and tissue trauma caused venospasm Mechanical stimulation of the carotid sinus in a human had no effect

These conclusions are based upon interpretation of an increase of the rate of perfusion under constant pressure head as indicating a relaxation of the veins

I think any physiologist not knowing of these results would have

Burton: I don't know if this is profitable, but I think you are confusing the idea of resistance. When you use the word "resistance," you have already eliminated the consideration of the pressure gradient from one end to the other. Dividing that by the flow gives resistance. Therefore, any more discussion of what happens to the pressure is irrelevant if I say the resistance has gone down. That means that the pressure head has already been taken into consideration.

Now I admit that in Dr. Coles' experiment the pressure was not measured at the heart end. But it is quite easy to see that, even if that had risen 20 mm. or dropped 20 mm. – and it could not have dropped that much because it was probably only 5 to start with – this change in pressure could not have accounted for a three- or four-fold increase in flow.

Fremont-Smith: In other words, it could move in that direction but could not account for that magnitude?

Burton: It could only be relatively minor in that direction.

Nickerson: How high was this perfusion pressure with respect to the venous pressure? Was it very much higher?

Burton: Yes. I was not directing this research, but I remember seeing that the bottle was about two feet high.

Remington. It seems astonishing when you are putting it into so large a vein as the femoral, because it is a normal vein. You would think it would make a difference to your resistance.

Burton: Just figure it out. You had, say, 34 mm. of pressure head from the bottle, and it is 5 mm. at the heart. That is a 29 mm. driving pressure. Now, if that 5 went down to zero or minus 5, it could not produce a threefold increase in flow without a definite drop of resistance, could it possibly?

Green: Dr. Burton, if you decreased the blood coming from other veins and also reduced the viscosity with hemodilution, could that not account for the entire change in resistance?

Howard: You are measuring the flow from one source. You are measuring the flow from a bottle. But if your flow distally is cut down, then the flow from the bottle would increase without increasing the size of the vein.

Shorr: Could a reduced blood flow through the limb have been responsible for the failure of the bed to fill?

Franklin: In all the many isolated veins which I have tested, I have found reversal by ergotoxine of epinephrine constrictor effects, and that is usually regarded as evidence of a sympathetic vasodilator innervation. If, therefore, in Dr. John Coles' experiments

Burch: The point we must remember is that the volume of the blood in a vascular segment or the entire vascular system must be equal to the luminal volume of the segment or entire system

Green: It would depend upon how you define a collapsed vein in the neck Is that vein smaller or is it simply not filled with blood?

Burch. Whatever the size of the lumen, blood will completely fill it

Green· The vein has potential capacity

Burch Regardless, the actual volume will be equal. Potential volume merely indicates the volume it can assume

Burton I assure you there is no escaping the conclusion that the resistance to flow of this vein has decreased, hence, the cross-sectional area available for the blood to flow through has gone up

Moore Take the reverse Suppose the patient has been in congestive heart failure If you ran that blood in, the flow rate would go down, wouldn't it, with the standard pressure, because the venous pressure to the right of the heart is way up?

Burton You are talking of a different level Start lower I am speaking about the hemodynamics Here the tube must be bigger because it now allows three times as much flow

Moore· I don't think that follows

Fremont-Smith It does not prove the tube is bigger, because you could have the blood being pulled out of it faster Any mechanism for reducing the resistance would increase the flow

Burton There is no method of decreasing the resistance which does not involve getting a bigger cross-sectional area

Fremont-Smith This is according to Poiseuille's law?

Burton Yes

Fremont-Smith Does that apply in that size vessel?

Burton· Yes

Fremont-Smith In that case, it would be impossible for the inspiration to flatten out a vein in the neck, to increase the rate of blood flow, or to lower its pressure, and, actually, inspiration does lower pressure So I would think that if the heart were taking away the blood faster, there would be a reduction of resistance in just the contrary way to that which Dr Moore brought up that if the heart went into decompensation, there would be an increased resistance

Moore And the reverse would take place with a full expansion in the venous bed to the right of the heart

Burch But remember, all he measured was the rate at which the drops fell

Moore I think you must differentiate between a gentle mechanical stimulus and a real irritant to the intima, because they are certainly very different In the Dibenamine-treated dogs, have you done eosinophil counts after bleeding?

Remington I have not

Moore We have thought of them wholly in terms of the adrenal medullary response, but if they are adequately Dibenaminized and not traumatized, you have interfered with their whole pituitary and adrenal cortex

Nickerson Dibenamine does not interfere with discharge of the pituitary and the adrenal cortex in response to a variety of stimuli (10)

Moore It all depends on what the stimulus is We have done some work in the laboratory on that point If the stimulus involves tissue trauma, the central nervous system is adequate to trigger the whole thing, but if it is just bleeding alone without injury, it is conceivable that there might be a difference in response, namely, Remington's type one

Nickerson: May I say a word about the pharmacology of Dibenamine which I think is pertinent here, bearing first of all on Dr Zweifach's observation that it takes a tremendous dose of Dibenamine to prevent the local constrictor reaction to epinephrine We have resorted to a variety of tricks in order to separate the vasoconstrictor from the vasodilator actions of epinephrine, since our data seem to indicate uniformly that there is no blockade of the vasodilator action We found that in the cat a dose of Dibenamine which reverses the pressor response to a small dose of epinephrine, one to two micrograms per kilogram, is really blocking only about 40 per cent of the vasoconstrictor action It is simply reducing the vasoconstrictor response to the extent that the residual is masked by the vasodilatation

Zweifach Is this true for both epinephrine and norepinephrine?

Nickerson We found that epinephrine and norepinephrine, as far as their vasoconstrictor action is concerned, are blocked in an exactly parallel manner (11) The difference in the blood pressure response after Dibenamine is due to the complexity of the response One of the experiments in which this parallelism was observed consisted of starting a continuous infusion of isopropylnorepinephrine, which had previously been shown to be adequate to produce maximum cardiac acceleration and maximum adrenergic vasodilatation We then superimposed injections of epinephrine and norepinephrine Under these conditions, when Dibenamine or one of its

there was *reflex* venodilatation, increased stimulation through venodilator fibers is an alternative or companion explanation to reduction in venoconstrictor stimulation. Without more details than we have yet had about Dr Coles' experiments, I may be irrelevant in referring to more localized venodilator mechanisms but I will take that risk The well-known dilator response of human superficial veins to tapping is found also in internal veins of man and lower animals (7,8,9), and among the reactive vessels is the abdominal vena cava of the usual laboratory mammals Normally, if the limbs are at rest, that vessel is considerably constricted as far proximally as the renal vein entries, but it dilates rapidly and markedly when it is tapped, and in one very constricted vessel Dr. McLachlin and I recorded a hundredfold increase in cross-section

The effect is not dependent upon long-distance nervous pathways, for in one animal I cauterized the whole circumference of the vein wall at two levels about 3 cm apart, this interrupted any nerve fibers passing to that section of vein, yet did not affect its response to tapping That such response is due to the internal bump of blood, produced by the tapping, on the vein wall was shown by a further experiment in which, after a tap, I kept my finger down on the vein until I felt the bump of blood on each side The result was not the usual uniform dilatation, but dilatation on either side of the still-constricted central part where my finger had been So the effect is locally intermediated I personally think that the abdominal vena cava in these laboratory mammals has its caliber automatically adjusted to the fluctuating venous return from the limbs, etc, through a synergy between this local dilator mechanism and the constrictor effects of circulating humoral agents and/or nerve impulses

To return to Dr Coles' experiments on dogs, if the femoral vein and abdominal vena cava were in the resting, constricted state, and he suddenly turned on the infusion under some pressure, that might well have dilated the vessels through the mechanism I have described But we have not had enough details about the experiments in question

Remington I can't see how this ties in with the venospasms that plague workers with an intravenous catheter

Franklin You mean in shock?

Remington No, in any individual

Franklin I can get veins opened quite easily

Remington But I have seen catheters stuck in veins so that they could not be moved

is actually decreased. Vasodilation, on the other hand, or failure of constriction, lowers the reserve blood in the large veins, and the heart is small This dog can take very little blood loss without a precipitous drop in flow and in pressure In that sense, I can remove only a relatively small amount of blood But pressure in that animal means something quite different from what it does in the normal He can withstand a very low pressure and recover from it

Zweifach In a publication on the hemodynamic effects of Dibenamine during shock (12), you compared the Dibenamine-treated animal with etherized animals subjected to shock Would you discuss that relationship?

Remington Ether, when given in large amounts, produces a lower resistance and a large flow The resistance of the etherized dog to hemorrhage is certainly reduced Of course, whether his ability to withstand low pressure has been increased or not, I don't know

Zweifach: The Dibenamine-treated animal apparently is resistant to the deleterious effects of hemorrhagic hypotension, because more blood can be perfused through the tissues in the face of a decreased peripheral vasoconstriction. Your hemodynamic measurements indicate that the etherized animal likewise fails to vasoconstrict Despite this fact, the animal cannot withstand hemorrhagic hypotension and dies much sooner than dogs subjected to shock, for example, under morphine anesthesia

Remington Of course, he has ether anesthesia in addition to the blood loss

Zweifach I believe that our observations on the omental circulation in etherized animals indicate a significant difference between these two groups of animals The etherized dog shows an ineffective compensation in the terminal vascular bed following hemorrhage There is only a minimal potentiation of the reactivity to epinephrine, vasomotion is not augmented, vasoconstriction, especially in the arterioles, is negligible The essential difference between Dibenamine-treated and etherized dogs subjected to shock is the continued operation of the terminal vascular bed as a dynamic functional unit in the Dibenamine-treated animal which is resistant, and the functional deterioration of the peripheral circulation in etherized animals which readily develop the irreversible type of shock

Remington I don't know why these dogs die

Zweifach In other words, taking into account all of the hemodynamic measurements which you made, and arbitrarily selecting a given point during the syndrome, you cannot predict whether

congeners is administered, responses to the two sympathomimetics are reduced in an exactly parallel manner. It is quite reasonable that there still should be seen a very considerable vasoconstriction in response to the local application of epinephrine at a time when the pressor response is reversed. The critical question here is whether vasoconstriction in various organs is blocked equally. Unfortunately, at the moment we have very little information on this point.

Remington: I should like to pick up this Isuprel response. I spoke of the response of a normal dog with a high reserve blood volume and a slow heart. After Isuprel injection, the cardiac index is high. In this process the central veins lose their pressure and the heart becomes small. In other words, the animal has translocated reserve blood out of the central veins and into the periphery. Because he has maintained an adequate pressure level in the arterial bed, the flow is increased.

As the Isuprel wears off, the flow returns to the initial level. Now suppose 5 ml. per kg. of blood is withdrawn. This does not change the heart rate, and the venous pressure may or may not have dropped a bit. The resistance is not changed. Now with a second dose of Isuprel, the cardiac index will not rise as far. As bleeding is continued, the point is reached at which, after Isuprel, the flow, which of course has been reduced because of the hemorrhage, returns to normal but not above normal. By this time the reserve blood has been severely reduced because of the hemorrhages. In the late stages of bleeding, the cardiac output may fall with Isuprel as the periphery opens, and there is no longer enough reserve blood to fill the expanded bed.

Next, let us take a dog that has been heavily Dibenamine-treated, but is holding a normal pressure. After Isuprel, the flow increases to high levels. As Isuprel wears off, the pressure usually does not return to normal, reflecting the loss in constrictor ability. After a 5 ml. per kg. blood loss from this relatively dilated animal, the flow increase is much less and is quantitatively comparable to that seen after the loss of, say, 30 ml. per kg. of blood in the untreated dog.

What I have been trying to imply is that the amount of blood that can be taken out of a dog is a function of the constrictor capacity of that dog. If the dog can constrict, I can get more blood out of him before his pressure falls to critical levels. But at the same time the constriction process itself, if prolonged, handicaps that animal, and results in death. If the constrictor activity is increased, as it is after trauma, or with intravenous epinephrine sustained throughout the hemorrhage period, the resistance to bleeding

to include, I asked Dr Scarff if he would give me his views, and he told me the conditions under which, in his experience, interference with the central nervous system of man produced shock There was none with removal of, or trauma to, the cerebrum as far down as the thalamus, or with increased intracranial pressure On the other hand, shock (defined as progressive fall of blood pressure and diminution in pulse pressure without primary fall of blood volume) occurred during marked operative interference in the region of the optic chiasma with attendant retraction of hypothalamic structures Manipulation of the brain stem, even at the supposed level of the vasomotor center, produced no effect upon blood pressure, though it could on occasion cause temporary, reversible respiratory failure Pain per se (for example, through trigeminal nerve stimulation) could result in hypopiesis after a transient hyperpiesis, and in such cases cocainization was required Further down in the central nervous system, some spinal cord concussions had resulted in low blood pressure, a few instances occurring among U S Navy personnel Dr Scarff did not say if the fall in pressure was progressive

I thought it might be useful to give these details, from a neurosurgeon's experience, about the central nervous system and shock The part played by the hypothalamus seems to me to be of particular interest

Shorr Thank you, Dr Franklin

Osserman I wonder if Dr Remington would mind commenting further on the results of the experiments in which he demonstrated that the administration of large volumes of intraperitoneal glucose (isotonic) resulted in hypersensitivity of the dogs to hemorrhage Is it conceivable that the glucose solution would draw sufficient quantities of sodium from the ECF and circulating plasma to result in a secondary water shift into the tissues, particularly into the central nervous system with resulting cerebral edema and "cerebral death"?

Remington I am in a most complete quandary as to why these animals die In many ways, it looks like a cerebral death As I said, these animals are vegetables The only animals I have seen like them have been in some cases of adrenal crisis

Burton I should like to make one fundamental comment in order to have Dr Remington qualify what he said about the ability to constrict largely determining the preservation of the reservoir of blood These figures are from Dr Green's compilations (13) I think it is 70 or 80 per cent of the volume of the circulation that is

these dogs are going to live or die, on the basis of such indices alone.

Remington No

Zweifach· However, if you then add indices of peripheral vascular function, such as those obtained in the mesenteric circulation, the predictability with reference to the ultimate fatal outcome of the experiment is definitely increased In terms of Dibenamine, we have another set of interesting data which we cannot explain We have found, of course, that in terms of the ability of an animal to withstand hemorrhagic or traumatic shock, that equally important are the compensatory mechanisms, and we feel that a contributing factor to adequate compensation is some renal factor.

Our routine procedure in arenal experiments has been surgically to remove one kidney and to place a loose, rubberized ligature about the renal pedicle of the second kidney This is done several weeks before the experiment The loose ends of the ligature are implanted under the skin At the time of the experiment, the ligature is exposed and tied tightly so as to exclude the circulation through the kidney At the end of the experiment, the organ is examined to determine whether any blood flow is present This has been adopted as the simplest procedure which would introduce a minimum of operative trauma at the time of the experiment

Hyman How long after you tie them off do you follow up?

Zweifach On the average, the renal pedicle is tied off about one to two hours before hemorrhage is begun We have carried out experiments in which the kidneys were tied off the night before We have no evidence to indicate that the precise time interval between the exclusion of the kidney and the hemorrhage is a major consideration

Hyman The point is that the period is not long enough to permit significant autolysis

Zweifach No

Fine These animals have no anesthesia or sedative?

Zweifach We have carried out arenal experiments both with and without anesthesia In the unanesthetized animals, the loose ties are exposed under procaine and the pedicle tied off This was done in dogs subjected to hemorrhage without systemic anesthesia and in rats subjected to drum trauma For our routine hemorrhage experiments, the animals are given light pentobarbital anesthesia

Franklin· I should like to pass on some remarks made to me last night by my host, Dr John E Scarff, a neurosurgeon in this city Having merely seen the title, "The Nervous System in Shock," of this afternoon's discussion and not knowing exactly what it was

hemorrhagic picture As I followed the description, there are three groups of animals, three categories one group of animals without Dibenamine, one group of animals with light Dibenamine, and one group with heavy Dibenamine If you bleed those animals, there is some end-point You either bleed them to a certain volume or a certain pressure What was the end-point used for the three groups?

Remington Controls were bled stepwise to 40 mm. Hg, and then a half hour was allotted If the pressure rose in this interval, more blood was taken, until the pressure would not rise within thirty or forty minutes

Green. That was the same point for each of the three groups?

Remington Yes

Green And your slightly and heavily Dibenamine-treated animals survive and the controls die?

Remington Yes

Green. Do you have any data on cardiac output, oxygen consumption, or venous oxygen tension in these experiments that would give us a possible metabolic clue to the cause of the deaths?

Remington There is no clue whatsoever on anything we measured as to why they died or lived Oxygen consumption shows the same pattern, flow is the same, pressure is the same, venous pressure is the same, EKG is the same

Burton How about blood volume? In the heavily Dibenaminized animal, the blood volume would be much higher, wouldn't it?

Remington Cardiac output is the same, and that is what I am interested in, not blood volume

Nickerson Actually, there is no difference in the blood volume of the controls and the lightly Dibenaminized animals

Remington No Well, there is always the question of how stringently we dare apply bleeding volumes We can say that this dog bled 40 ml per kg, and the next dog bled 45, and that the average bleeding volume for a series of dogs is, say, 38 ml per kg Yet what really counts most is the last 1 or 2 ml per kg of blood loss The major part of the bleeding volume figure is set by the hemorrhage that can be taken before compensation sets in and also before compensation fails In the lightly Dibenaminized dog, the average blood loss is slightly under that of the control, but not significantly so I cannot, however, dogmatically conclude that the vascular stress is absolutely the same as for the controls

Fine Is it perhaps a critical drop in cardiac output that is involved in that last 5 to 10 ml?

Remington Yes, it probably is

on the venous side of the arterioles, so that this ability to constrict, which may be so important, must be thought of as an ability to constrict on the venous side of the arterioles This further reinforces my feeling that the answer to many of these problems lies in the venomotor system A constriction of arterioles could not supply very much to the reservoir of blood There is so little of the total blood volume on that side.

Remington By implication, I meant the aftermath of an arterial constriction.

Howard: I should like to ask Dr Remington if he has any idea as to why the patient with an acute pancreatitis or retroperitoneal hemorrhage, but particularly pancreatitis, may go into severe vascular collapse, and yet in a patient with the same disease but of lesser extent, blocking of the adjacent sympathetic might seem quite beneficial Can you think of any reason why inflammation in the pancreas should lead to a profound vascular collapse?

Remington What is this syndrome?

Howard An absent blood pressure, a fast pulse, death

Fine· I can give you some experimental data, if you like, that might bear upon it If you produce experimental pancreatitis by injecting sterile bile into the pancreatic duct by pressure, you kill the animal every time When you examine the animal during the process of dying, he shows widespread inflammation, including bacterial peritonitis If you protect that animal with aureomycin, he will go through the process of acute pancreatitis If you examine that organ several days later, it shows acute hemorrhagic pancreatitis, and then six weeks later, having recovered as a result of the aureomycin, he will show a shrunken pancreas So he has been through the acute pancreatitis, but apparently it has not hurt him any The superimposed septic process is apparently the factor which makes the difference between the chemical pancreatitis induced by the injection of bile and the septic pancreatitis which is called forth Therefore, sepsis could explain the shock in these patients Transfusion might not be of any use in such a situation, or perhaps of no more use than to take care of the loss in blood volume induced by the peritonitis, but that would not be sufficient to take care of the septic process superimposed

Shorr Dr Green, would you talk on the question of the regulation of the nervous system's participation in shock?

Green I do not have any particular comment, but I do want clarification on the experiments Dr Remington spoke of There were so many interruptions that I did not quite follow Let's stick to the

hinge on the extent to which any reduction in blood volume interferes with the renal blood flow. Studies (14,15) have pretty well established that the drastic hypotensive level we employed in the Dibenaminized animal is sufficient to curtail the renal blood flow completely in an ordinary anesthetized animal. Correlated with the absence of renal blood flow in the ordinary dog is the progressive disappearance of the renal vasoexcitor principle in the blood stream and the inception of the decompensatory phase, as observed in the vascular bed and in the appearance of ferritin in the blood. The one exception to this sequence is seen in the unanesthetized animal which, at the same drastic hypotensive level, continues to flood the blood stream with vasoexcitor material and continues to maintain an intact liver VDM mechanism. There is no release of ferritin and no interference with the inactivation capacity. Therefore, although experimental data are lacking, we think that there must be a small but effective blood flow in the absence of anesthesia, sufficient to release vasoexcitor material constantly from the kidney. The same situation appears to result during shock in the Dibenaminized animal. We feel that at least one of the consequences of the improved blood flow is the maintenance of some type of circulation in the kidney. The hypoxic kidney forms VEM continuously and releases it into the blood stream. The peripheral vascular bed still responds by the compensatory devices it normally exhibits, and it helps to maintain a sufficiently adequate blood flow to the liver so that it is protected from a degree of hypoxia which would lead to ferritin release and a deterioration of the inactivation mechanism. We would all agree that Dibenamine is no longer protective if given after the period of hypotension. It is a matter of prevention, and, we believe, a prevention of the deleterious effect of hypoxia as measurable by these two participating vasoactive principles.

Green. That sounds like a good hypothesis, but I am worried about Dr. Remington's results here. If that is the case, then surely if you compare the non-Dibenaminized animal with the Dibenaminized animal at 40 millimeters mean pressure, the Dibenaminized ought to have a significantly higher cardiac output and a higher oxygen uptake per minute. Yet, if I understand Dr. Remington correctly, there was no difference. So, if the cardiac output is the same but the renal blood flow is greater in the Dibenamine-treated animal, what part of the body is being deprived of blood?

Franklin. The renal flow need not be very great, need it?

Shorr. No, it need not be very large.

Green. The kidney has about a quarter of the cardiac output

Sharpey-Schafer. What about cerebral blood flow? Can you talk about that?

Remington No The measurement of cerebral blood flow in the dog is a hard proposition, because the carotids furnish skin and neck muscles as well as brain It is an intriguing problem

Green Did you have evidence of any difference in function of any organs? Was there a difference in renal function between your animals treated with Dibenamine as compared with the animals not Dibenaminized? We know that if you bleed an animal down to 40 or 50 mm Hg, or anything much lower, he doesn't put out any urine

Remington All I know is that the bladders were small when the experiment was discontinued, and that does not mean much

Green Do you care to speculate where vasoconstriction and vasodilation occurred, and what conclusions can you draw from your observations?

Remington Other than the conclusions already given, we are vague I do not know where this constriction is and I do not know where the dilation is because we simply cannot piece together the story as it is now developed We cannot answer why all the peripheral tissues in which flows have been measured show constriction and yet the general resistance does not I do recognize a cardiac index of 1 L per min as critical If the flow reaches this value, the animal is usually doomed But flow levels somewhat above this may also lead to death, and the diagnosis cannot be made from the flow level

Stead Did you run into the question that all measurements have to be multiplied by time? That comes down again to the factor you mentioned, that it is the last part of it that counts You can take cardiac output data which may not be significantly different as you look at them in absolute terms, still, if you multiply by hours, it might make the difference between life and death

Fine: That is my point, too The crucial factor in the death of these Dibenaminized animals may not be referable to what is going on in the peripheral circulation, but to an effect upon cardiac output

Shorr We have been impressed with what might be considered a selective protective action of Dibenamine In focusing our attention on liver and kidney, we have obtained at least indirect evidence that the nature of the blood flow in the Dibenaminized animal, with its excellently maintained peripheral vascular compensatory reactions, may represent one of the important determinants of survival Much of this protective action would seem to

Nickerson I wish we could say that Dibenamine has no actions other than adrenergic blockade That, of course, is what the pharmacologist is always striving for, the perfectly specific agent, and he has always fallen short. When administered in the usual blocking dosage, the primary action of Dibenamine and its congeners is to block excitatory responses to the adrenergic mediators, whether they are circulating in the blood stream or are released locally by nerve endings (18) Inhibitory responses are essentially unaltered, that is, the relaxation of vascular or other smooth muscle is not prevented In the usual doses these agents do not have detectable direct effects on the vascular system They do have some direct central nervous system stimulant action, particularly when they are given rapidly in large doses intravenously Some of the congeners, including 688A, have a certain amount of antihistaminic action

Stead I merely wondered if, when these drugs are studied under a greater and greater variety of conditions, they will not be found to have actions which are not fully mediated through the nervous system

Howard Dr Stead, aren't we probably talking about the same thing that clinicians have noted repeatedly? That is, that a patient who is in a state of acute alcoholism goes into profound hypotension with minimal trauma Isn't this in all probability a peripheral vasodilator mechanism that is comparable to the Dibenaminized animal?

Stead I wouldn't have guessed so I have a feeling that alcohol makes the cells themselves sick I doubt that the effects of alcohol are based purely on the autonomic nervous system

Nickerson I cannot answer your question regarding the future studies, but to date these agents have been studied on quite a variety of systems and as yet no important direct action on smooth muscle has been demonstrated I should like to add one more pharmacologic action of Dibenamine The group in Houston (19) has demonstrated that Dibenamine reduces the sensitivity of an animal to potassium, in the sense that Dibenamine allows the administration of much larger doses of potassium before electrocardiographic changes and death occur Whether or not this phenomenon has anything to do with the other actions of Dibenamine, I do not know The authors provided no explanation of the mechanism of this effect and I have none to offer

Franklin I wonder whether the vasopressor agent of cerebral origin described by Taylor, Page, and Corcoran (20) has any

Shorr: It doesn't have to have that much, and probably it has less in the state of shock in the absence of anesthesia, but apparently it has enough to release the vasoexcitor continually The vasoexcitor, once in the blood, disappears fairly rapidly unless it is constantly replenished

Bradley: If that hypothesis is correct, I should think that pyrogens or quinine or other agents that bring about vasodilatation in the kidney might exert a protective action

Zweifach The possibility remains that pyrogens or other vasodilator agents might damage the kidney and thereby limit its positive contribution to vascular compensation

Bradley· I have the impression that patients who have fever do less well when subjected to trauma

Zweifach: These agents probably do not have a selective action on the kidney, but in addition may affect the blood vessels in other organs

Shorr I should imagine if the pyrogens were really effective in opening the bed widely, that they might be deleterious As Dr Franklin said, no one has measured the blood flow – and it certainly ought to be measured – in the kidney However, I don't think it has to be great, possibly 10 per cent of the normal, as long as it permits a constant release of vasoexcitor material into the blood

Bradley Does Dibenamine cause vasodilation or vasoconstriction in the kidney in normal animals?

Nickerson I do not know of any data which indicate that. In dogs, the effect of Dibenamine is variable The kidney, in a normal animal, appears to have an intrinsic regulatory mechanism that is stronger than Dibenamine in a sense If you inject a large intravenous dose of Dibenamine very rapidly so that you essentially produce mild shock, the renal blood flow goes down, but the filtration fraction goes up, and the glomerular filtration rate remains within normal limits (16) Other workers (17) have recently shown that blocking doses of 688A, carefully administered, may produce a significant increase in renal plasma flow without a change in the glomerular filtration rate Under conditions of normal vasomotor tone, Dibenamine and its congeners have only a minor effect on renal hemodynamics

Stead I should like to ask Dr Nickerson one question in regard to the simplicity of these compounds I take it from the discussion we have heard today that these are very simple compounds that block the autonomic nervous system and have no other action Or do these have more complicated effects on the blood?

point of view, his use of sodium pentobarbital is more of a blow And I don't know why anybody should think 54 ml per kg is just too much for the animal

Moore Dr Shorr, what is the nature of the stimulus that results in release of VEM from the kidney? Is it hypotension itself?

Shorr Unfortunately, *in vitro,* where we theoretically can control conditions, we are limited in our exploration of the factors that regulate metabolism We can talk with most certainty about the effect of altering the oxygen tension in the media of the *in vitro* experiment Using a standard kidney slice, reduction in oxygen tension to about 20 per cent, as against 100 per cent, leads to a degree of tissue hypoxia which invariably causes release of VEM

Moore Can you release VEM in a normal dog by suffocating it?

Shorr. Yes, by suffocating its kidney.

Moore I know, I mean by suffocating the dog

Shorr We have not done that We have exposed a normal human to breathing a mixture of 10 per cent oxygen and 90 per cent nitrogen (22) After about fifteen minutes, with a catheter in the renal vein, we were able to detect VEM When the oxygen tension was increased, the VEM disappeared from the renal vein blood in a comparatively short time So that we do know that altering the oxygen tension –

Moore "Oxygenization of tissue" might be a better term Oxygen tension may be quite normal in a shocked animal

Shorr Yes, it is the average oxygen delivered to the tissue in relation to the oxygen need

Moore Right

Shorr That is the one stimulus we can be sure of Whether some type of neurogenic stimulus is necessary, or can equally well lead, to the delivery of VEM, we do not know

Moore Is VEM diffusible through cellophane?

Shorr Under certain conditions

Moore Do you want to give any crude estimates of its chemical characterization?

Shorr We should be very glad if we were able to do that

Moore But it will pass through ordinary cellophane?

Shorr Anything that we might say at the present time about the molecular size or the chemical nature of VEM would not be founded on reliable evidence

Moore But you certainly regard it as protein in nature or somehow or other linked to protein?

Shorr We think it is protein in nature or linked to protein

relevance to our subject.

Nickerson: Raab (21) has been talking for several years about a pressor agent of cerebral origin, usually obtained from nervous tissue by extraction procedures. I believe he calls it encephalin. It seems to have many of the properties of epinephrine. I do not believe there is any evidence at the moment to indicate that this is the type of agent with which Page's group is concerned.

Haley: When you go over the data of Page's group, they are not, at least to me, convincing. They did two or three experiments and obtained certain effects, maybe if they did the other eight or nine, the results would not be the same. But they have a lead which should be pursued. There is one question I should like to ask about Dibenamine. It is a derivative of nitrogen mustard, and there are a number of other blocking agents, excluding the ergot alkaloids, which are in some instances much simpler compounds. I wonder what effect they would have in shock and if they have been tried, and also if nitrogen mustard itself has been tried.

Shorr: Has anyone worked with these agents?

Fine: We have worked with a variety of agents but have never had any definitive results. I am not speaking now of transitory effects on hemodynamics. We were looking for clear-cut results, such as prevention of irreversibility or recovery from irreversibility, but we did not find them.

Moore: Including Dibenamine?

Fine. We did some priming of animals with Dibenamine and got some differences, but nothing indicated with finality that there was a substantial difference in the outcome.

Zweifach: In your experimental procedure with a self-infusion reservoir, the animal is subjected to a massive bleeding immediately up to 54 ml. per kg. and then maintained at a drastic hypotension of about 30 mm. Hg for a period of several hours. I am not certain that this type of procedure will bring out the difference between normal and Dibenaminized animals, since the Dibenamine-treated animal cannot withstand massive exsanguination.

Fine: We bleed two groups of animals to the same extent and one group survives, moreover, they survive without any difficulty. There is no question about the fact that the survivors have not suffered any permanent damage.

Moore. You mean by a liver perfusion?

Fine: No, by the antibiotics. Dr. Zweifach speaks of the extreme degree of hypotension we subject them to, and he thinks that is too much of a blow. He does not consider the fact that, from my

normal animal and the sympathectomized

Zweifach So far as we can tell, the compensatory response in the terminal vascular bed, referable to the release of renal VEM, is of the same order of magnitude in both normal and sympathectomized dogs subjected to hemorrhagic shock

Shorr The rat test shows plasma VEM of the same order of magnitude, although the level of the hyperreactivity in the omentum of the sympathectomized animal in shock is modified

Green Would it be possible to get a quantitation in renal vein blood where there is a higher concentration to start with?

Zweifach Although the omental vessels in the sympathectomized animal show a higher basal reactivity to epinephrine than controls, the blood of such animals does not contain appreciable titers of VEM We, unfortunately, have no studies on renal blood in the normal as compared with the sympathectomized animals subjected to shock

Nickerson As I understand it, the primary difference between the shock picture in sympathectomized and Dibenaminized animals and the controls is in the VEM production or release

Zweifach The major difference between the protected animals and controls lies in the continued perfusion of the tissues with blood, despite the drastic hypotension, thereby preventing vascular deterioration and its metabolic consequences

Green Do you feel that it is due to greater release of VEM?

Zweifach I do not believe it is possible for us to state unequivocally that the greater resistance of sympathectomized and Dibenamized animals to hypotension is specifically related to VEM

Moore Have you done any experiments on dogs with severe peripheral trauma without shock? We talk so much about trauma and shock, but we ought not to forget that trauma without shock incites a whole train of physiologic adjustments tachycardia, hyperglycemia, and oliguria, for instance, not to mention the whole adrenocortical chain of events, even though there is no alteration in blood pressure as a result of the trauma With that sort of what might be called "threshold stimulus," do you see VEM coming out?

Shorr Evidence has recently been found by Taquini and his associates that renin production by the kidney is under the influence of neurogenic mechanisms and that an intact nervous pathway is necessary for maximum renin production (23)

Nickerson I believe we can assume that stimulation of the sympathetic nerves to the kidney can bring about almost complete cessation of the renal, or at least cortical, blood flow Under almost

Moore. You have never been able to precipitate protein out of plasma and have VEM the supernatant?

Shorr. No, but that does not tell us anything because it could be occluded in the protein precipitate

Burton What is the nature of the relation between VEM and renin? Being an outsider, I am a bit puzzled that you never mentioned renin It couldn't be the same thing that you are working on?

Shorr Our inability to characterize VEM chemically makes it difficult to differentiate between renin and VEM Hypertensin, the active product of renin and its globulin substrate, is musculotropic It probably acts on the arterioles rather than on the capillaries We are hoping soon to procure one of the new highly purified renin preparations to see whether it is devoid of activity on the terminal vascular units upon which VEM acts The renin preparations we have tested so far have always had some VEM activity, but entirely unrelated to their renin contents In other words, two preparations with the same renin content might be associated in one case with very low VEM activity and in the other with high VEM activity It appears as though the methods for the isolation of crude renin preparations are such as to carry along variable amounts of VEM I think that with the purer products which are being made in other laboratories today we shall soon be able to tell whether or not renin-hypertensin systems are entirely devoid of the kind of activity which characterizes VEM

Burton Does the Goldblatt clamp on a dog make that dog produce VEM?

Shorr The Goldblatt clamp leads to the rapid production of VEM and its continuous release into the circulation

Moore: And the same thing is true of a coarctate clamp anywhere along the aorta, I suppose?

Shorr: We have not varied our technique

Moore. How about laboratory coronary occlusion?

Shorr We have no information on that

Moore But just reasoning by extrapolation, you would predict that they would do this?

Shorr Anything that would interfere with renal blood flow would presumably do so

Nelson Dr. Shorr, do you believe that the diminished production of VEM in a sympathectomized dog in shock is due to an alteration of the "normal" renal ischemia which ensues?

Shorr: No, the release of VEM is quite orderly. There is no reason for thinking that any quantitative difference exists between the

situation Very soon after the application of a Goldblatt clamp, VEM appears in the blood There is no reason, from any of our work, to feel that this should do anything to restrict the circulation in the liver, but after a few days or a week or so, the opposite member of the team, ferritin, begins to appear in the blood There has been no hypoxia, and yet the metabolism of the liver has been altered to allow the release of enough ferritin to approximately balance the VEM This results in a neutral plasma reaction, with high concentrations of both VEM and ferritin present (24) The presence of a metabolic defect in the liver is revealed by the fact that, whereas in the normal liver all the ferritin occurs in the inert disulfide form, in the hypertensive liver, about 15 to 25 per cent of the ferritin is present in the vasoactive sulfhydryl form (25) There is evidence, therefore, that the presence of the opposite factor, VEM, apparently without the introduction of an anoxic or hypoxic element, can alter the ferritin metabolism of the liver

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all conditions which have been studied, this would bring about the release of VEM

Shorr. Yes

Moore That is exactly what I am talking about

Nickerson I believe it is a fair bet to assume that VEM is released under these conditions

Shorr. That is right

Nickerson But that does not mean that it is released by a neurogenic action

Shorr In order to clarify this point, it would be necessary to have a type of neurogenic stimulation which is devoid of vasoconstrictor effects

Moore I do not care whether it is neurogenic, but there is an amount of stimulation where hypoxia, in the sense of decreased delivery of oxygen to tissue, is a result of something other than hypotension

Shorr Yes

Moore Maybe it is not neurogenic

Shorr Perhaps Dr Haley would tell us about his animals in which he found that, following the initial VDM predominance, there occurred a stage in which hyperreactivity developed

Haley If you wish to take the stand of recognizing radiation as being a trauma, you get, from the third to the fifth day, the appearance of massive quantities of VDM On the sixth day those quantities are decreased, and on the seventh day the response is at the normal level This is both in the capillary bed of the irradiated animal and in the blood taken from an irradiated animal on those days and tested in a normal animal

From the eighth to the twelfth day, there are increasing quantities of VEM, and from the twelfth to the nineteenth day, the amount of VEM decreases.

Unfortunately, hemorrhage starts on the third day, so we are probably dealing again with some phase of shock But what I cannot understand is why we get the VDM first and the VEM second

Moore Why do you say that because hemorrhage starts you are dealing with some phase of shock? That is interesting

Haley. Well, in the first place, you have a hemoconcentration on day three, and a massive hemorrhage into the gut

Moore And you mean the animals go into shock as a result of it?

Haley Yes, they go into shock

Shorr. We have observed what is apparently the reverse of that

ACUTE AND CHRONIC HYPOTENSION AFTER HEMORRHAGE IN MAN

E P SHARPEY-SCHAFER
Department of Medicine
St Thomas' Hospital Medical School
London, England

FAINT INDUCED BY ACUTE VENESECTION

For some years we have been interested in the effects of hemorrhage in normal man These are somewhat different from the effects in animals, about which we have already heard If you remove enough blood from any normal man, he will faint The sequence of events is that the blood pressure is maintained for a period, and then suddenly falls to a low level, and the heart rate slows As the subject is bled, the filling pressure, or rather the pressure measured in the auricle, falls and the cardiac output goes down, but with an acute fall of blood pressure there is either no change in cardiac output or a slight fall Occasionally, the output appears to rise slightly In other words, the change in blood pressure cannot be ascribed to a change in cardiac output It must therefore be due to a change in peripheral resistance (1)

Moore And I suppose a syncope-like attack, although the patient might not have lost consciousness with only a small venesection

Sharpey-Schafer There were cuffs on the thighs over that period, which amounts to a hemorrhage of perhaps 500 to 600 ml

Moore Would you describe that as a common result of your cuffs plus venesection?

Sharpey-Schafer Yes, it is quite a standard method for inducing a faint If one is prepared to bleed as much as 1500 ml, I think 90 per cent of men will faint. If the faint is severe, retransfusion of venesected blood may take an appreciable period, whereas, if there are cuffs on the thighs, they can be deflated and the subject will recover quickly

Moore It is not quantitative, you really do not know what the stimulus has been unless you have plethysmographic recordings on the legs

Sharpey-Schafer I know, but in many subjects the experiments were done with venesection only

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Sharpey-Schafer I know, but in many subjects the experiments were done with venesection only

Stead How many times have you done the same experiment on the same person?

Sharpey-Schafer Certainly a dozen times

Stead The subjects always faint?

Sharpey-Schafer Eventually, yes They may faint with different amounts of blood loss

Stead I would have thought, from the things that we have done, that this does not really have anything to do with removal of the blood

Moore: That is the question I was raising, because there is a response like that, as well as many interesting transcapillary readjustments, with only 500 to 750 ml. of actual bleeding if the patient is in a vertical position at the time

Sharpey-Schafer There is great variation, in my opinion, in the response of individuals, or of the same individual on different occasions

Moore I am sure that is true

Sharpey-Schafer Some people you need not bleed at all, you have only to approach them

Moore Just show them the needle

Sharpey-Schafer We approached, with a needle, a normal subject in whom we were measuring forearm flow and blood pressure. He was not actually touched, but he fainted with vasodilatation in muscle vessels

With the acute fall of blood pressure there is usually an increased flow in the forearm during the height of the faint If the blood pressure falls to very low levels, the flow may not change greatly These results indicate that there is vasodilatation in muscle vessels This observation is not new It was described by Hunter well over two hundred years ago He observed that during the faint the blood in the forearm veins was bright red This reaction in muscle vessels is abolished in the sympathectomized limb (2)

FAINTING ACCOMPANYING THE VERTICAL POSITION

There are a number of methods of producing this fainting reaction, which are similar to a fairly large hemorrhage For example, there is standing in the erect posture Normal subjects show constriction in the forearm vessels when tipped from the supine to the erect position (3)

Howarth and Edholm (4) bled normal subjects lying flat and measured forearm blood flow Rather curiously, although the subjects might faint eventually, there was not the initial constriction in the forearm that might have been expected One reason may be

that the rate of bleeding was not fast enough On the tip table, when a subject is moved from the supine to the erect posture, the rate of change of distribution of blood is rapid, a matter of a few seconds, whereas in most venesections it is difficult to bleed at rates much more than 100 ml a minute We succeeded in bleeding one subject 850 ml of blood in three minutes, and he showed constriction

Moore· What about his pulse rate?

Sharpey-Schafer It increased slightly Some people don't accelerate at all

The constriction in forearm vessels in the erect posture does not occur when the limb is sympathectomized (3) Subjects who faint easily show vasodilatation in forearm vessels coincident with the blood pressure fall when maintained in the erect posture

Among additional factors which increase the incidence of fainting are heat and the extreme lordotic position, as in standing at attention In this posture there appears to be an obstruction to the inferior vena cava at the level of the diaphragm (Figure 8)

To sum up the situation in regard to fainting, as far as we can see, if you bleed a normal unanesthetized man, either flat or in the erect posture, and bleed him enough, he will always faint We think the fall in venous pressure produced by bleeding probably has something to do with the afferent pathway of the faint reaction, and that it may be initiated somewhere in the heart

There are a number of things we do not know about it The efferent pathway seems to be the vasomotor nerves We know very little about the afferent side.

FACTORS AFFECTING THE FAINTING REACTION

If the same procedures are used in subjects with congestive heart failure, who already have a high venous pressure, then fainting does not occur I do not believe anybody has ever seen a spontaneous faint with muscle vasodilatation in an established case of congestive heart failure with an originally high venous pressure, which is remarkable when you think of the number of needles that have been inserted into patients with congestive heart failure

It is questionable whether fainting occurs in other species Howarth has some evidence on what happens in the rabbit I wonder whether any of you have ever seen bled dogs suddenly produce bradycardia, because it is very difficult in animals to attempt to measure muscle blood flow

The other point I should like to make is this We have never yet seen this type of reaction to hemorrhage under full anesthesia

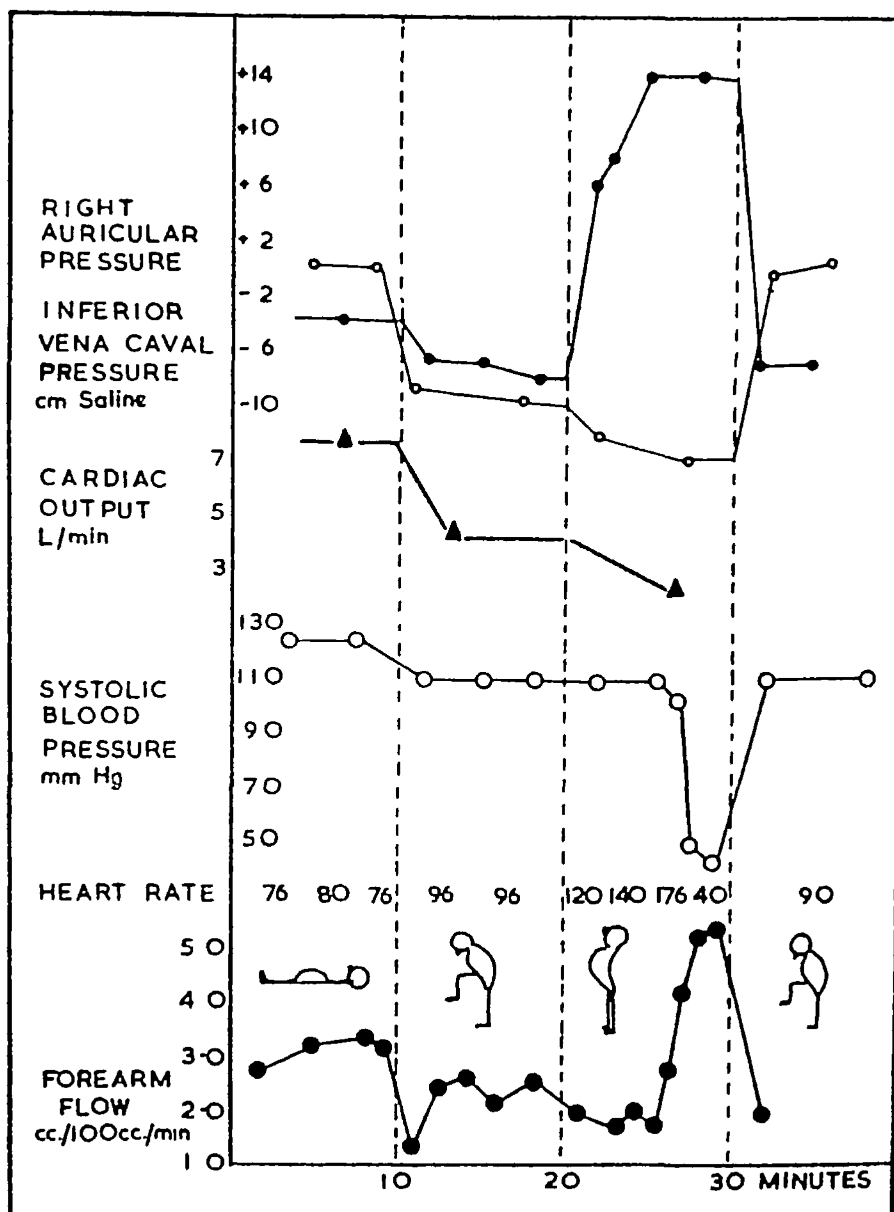


FIGURE 8 Data from a subject who fainted in the extreme lordotic posture

I agree that we have not had a great number of cases in which forearm flow was measured, so that I would not say that it never occurs All I can say at the moment is that we have not seen it But I strongly suspect that anesthesia abolishes this reaction in man.

Moore. The response to turning a patient under spinal anesthesia is a reaction to acute hemorrhage.

Sharpey-Schafer That is more complicated. In the upper part of the body when the blood pressure goes down, there is a period

of muscle vasodilatation If a patient was given a spinal anesthetic and maintained in the vertical position, I don't think he would continue to live

Moore When a patient under spinal anesthesia, who is stabilized in a supine position, is turned into the Sims's position, there is quite a characteristic drop in blood pressure and his heart slows We have always thought it was a reflex phenomenon, in other words, purely due to gravitation and a huge, denervated vascular bed

Sharpey-Schafer. I think it is, but I am merely pointing out that there may be an additional factor because in the upper part of the body there is muscle vasodilatation as well

Moore Why isn't it almost exactly the same problem as the paraplegic?

Sharpey-Schafer I think the problem in spinal anesthesia and in the paraplegic is the same

Fremont-Smith The thing that would be inhibited by anesthesia is the muscle vasodilatation

Sharpey-Schafer I think so, yes

Moore Would it be abolished by general anesthesia?

Sharpey-Schafer. That is right, not by spinal

Moore I think spinal is almost a daily set-up for this type of hypotension

Sharpey-Schafer Yes

Moore It is important to recognize it surgically It responds beautifully to Neosynephrine

Fremont-Smith As a mechanical way of avoiding this, did you ever try binding the limbs with bandage so that the muscles would be fairly well compressed and unable to take up very much blood, couldn't get a hemorrhage into them, so to speak?

Sharpey-Schafer We have not tried that It is difficult to do It would be necessary to show that the faint occurred and was then abolished by compressing the limbs

Fremont-Smith Could you take someone who characteristically fainted? If you bound such a person, perhaps the next five times he would not faint That would give you a lead, especially if you had the bradycardia, also

Sharpey-Schafer Bandaging does modify things If you put it on at a moderate pressure, I would say yes

Fremont-Smith You can inhibit it that way

Sharpey-Schafer Yes If the subject starts to move about, he will not faint, when he quiets down a bit, he may then do it

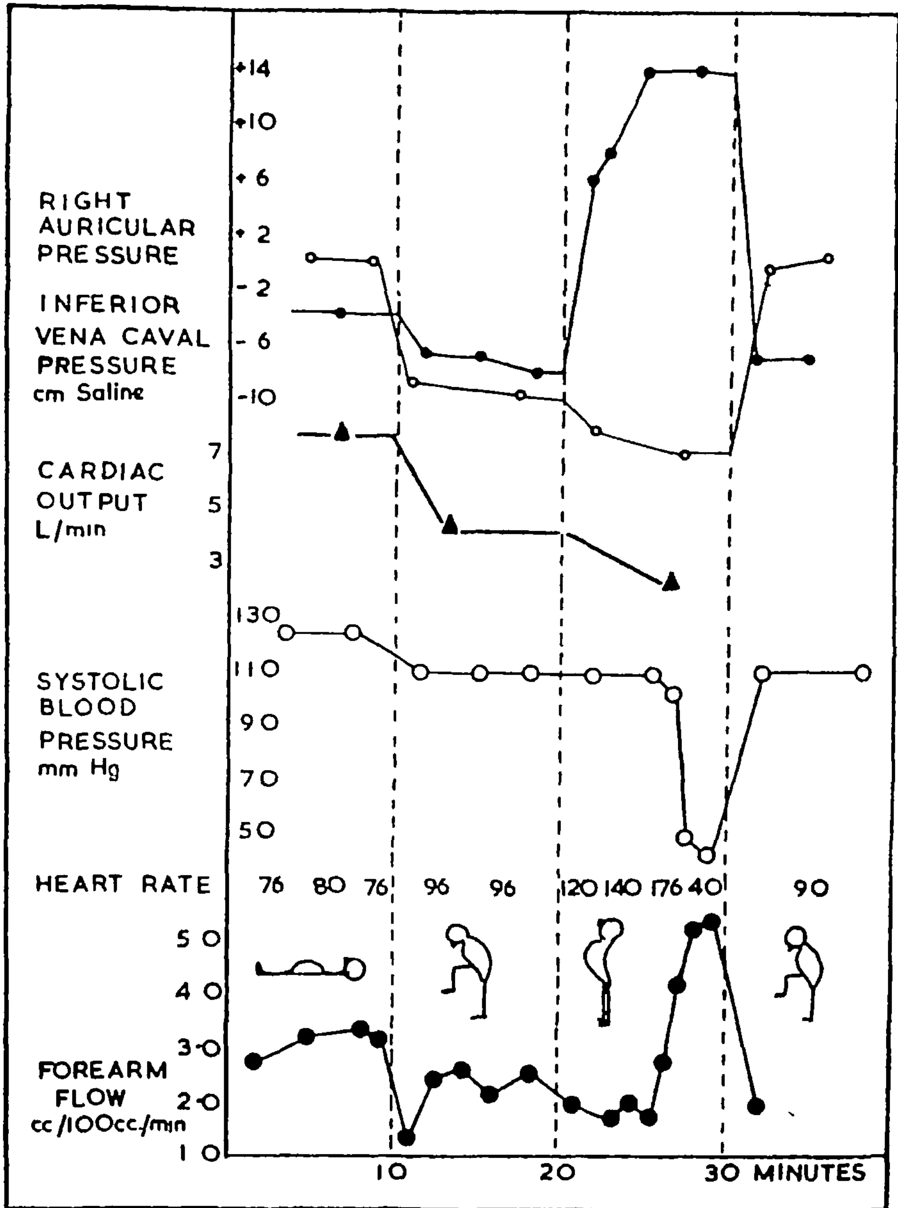


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Bradley Did you give any of these patients atropine?

Sharpey-Schafer. And faint them? Yes, that has been done

Stead. Leaving out the question of changes in rate, do you think there is a cardiac factor, also?

Sharpey-Schafer. I should say in the majority of cases the output is lower than it was when they were normal

Stead Let's take people who faint without bleeding, exactly the same people except you have not bled them I am a little skeptical myself that bleeding has anything to do with it, so let's just take the nonbleeding group

Sharpey-Schafer There is a discrepancy in our knowledge here. It is a technical difficulty. With the spontaneous fainters, the difficulty is to get all the recording apparatus into them without their fainting We know that they have muscle vasodilatation with the faint What precedes that, we do not know It is possible that there is a dilatation somewhere else, and it is still a bleeding mechanism For example, it is well known that those people faint more easily in the erect posture than the supine

Burton Would you care to mention the pituitary?

Sharpey-Schafer The pituitary may be fired by any of these methods (5) We think it is only a question of how low the blood pressure goes For example, the Valsalva maneuvers, which represent a different mechanism of producing hypotension in man, may cause pallor for about three-quarters of an hour afterward, and no urine may be passed for nine hours

Shorr Drs Whedon, Deitrick, and I (6) had some experiences which may be relevant We immobilized a group of healthy adults in casts which were placed around their lower extremities and body up to the thorax We followed their responses to being placed on a tilt table, the casts being removed during the test, throughout a six to eight week period of immobilization They proceeded to faint with increasing rapidity We were able to prevent fainting by binding their lower extremities We then repeated the same experiment with the same group of subjects with this one variation, that they were placed on a rocking bed throughout the period of immobilization This bed oscillated over an arc of about 24 degrees every three minutes During this second study period on the oscillating bed, their responses to the tilt table procedure were just as good as during the control period of ambulation

We could not be sure just what was responsible for the differences in their responses to the tilt table when they were immobilized in the fixed bed as compared to the oscillating bed It was apparent

that with each oscillation, there was pressure on the downward swing on the heels and that this was accompanied by a slight contraction of the leg muscles The patients were on the rocking bed from eight to eleven hours a day. Throughout this prolonged period of oscillation the continued muscular contractions, though slight, were believed to have improved muscle tone and hence peripheral vascular tone

Sharpey-Schafer. You didn't measure anything else?

Shorr We made a number of other observations Circulation time was unchanged during immobilization and there was a fall in the total blood volume which averaged 4 3 per cent during the oscillating bed experiment and 5 7 per cent in the fixed bed experiment There was a slight increase in heart rate averaging 3 beats per minute in the oscillating bed and 4 3 beats per minute in the fixed bed Resting arterial, systolic, and diastolic blood pressures did not change significantly During the tilt table studies, the most sensitive criterion of an impending faint was the fall in pulse pressure to critical levels of 10 to 12 mm Hg

Sharpey-Schafer Originally the critical pressure of their heart and cardiac output probably dropped to lower levels, and afterward they did not drop so easily I think that might well be so Apparently a vasoconstrictor component is in this somewhere, as is illustrated by the fact that acute hypotension from a small bleeding is potentiated by a blocking procedure

Nickerson Do you have any information on what vascular beds are involved in this vasoconstriction?

Sharpey-Schafer· Various people with various techniques have measured what is going on elsewhere Bearn, Billing, Edholm, and Sherlock (7) measured liver blood flows during fainting During the bleeding, the flow went down During the faint, it either did not change very much, or it dropped a little, and calculation suggested that there might be a slight decrease of vascular resistance, but I personally think that it is difficult to make such calculations on their data

In our group, de Wardener and McSwiney (8) have made similar measurements on the kidney, and I could sum it up by saying that the results are the same as in the liver

Nickerson We feel that the role of vasoconstriction is prior to the time of the actual faint, during the period when the organism is trying to prevent it

Sharpey-Schafer Yes But calculation of resistance in various parts of the body suggests that there is enough muscle vasodilata-

tion to account for the fall in blood pressure

Burton. The skin is quite constricted all through, very pale

Sharpey-Schafer. Yes There is probably actual constriction in the skin.

Bradley You feel sufficiently secure in the cardiac output data to say that cardiac output does not drop at all?

Sharpey-Schafer· I think it does drop

SEQUENCE OF EVENTS ACCOMPANYING FAINTING

Bradley Which comes first, the fall in the cardiac output, the decreased resistance, or syncope?

Sharpey-Schafer The sequence of events is fall in cardiac output, then suddenly muscle vasodilatation; the exact timing of the bradycardia and the muscle vasodilatation have not as yet been established It is a question of continuous records, the difficulty being that it takes a second or so to measure any blood flow, because you have to put on a collecting cuff and measure the rate of volume increase

Bradley. You think it is possible, then, that the blood pressure falls initially with syncope because the cardiac output suddenly falls?

Sharpey-Schafer There is usually some fall in blood pressure as the person bleeds It is not usually very great The great fall in blood pressure occurs with the muscle vasodilatation

Stead There is a striking fall in peripheral resistance and much less change, if any, in cardiac output At first glance, then, one says that the reaction of the heart is not important in the faint However, one of the most striking effects of peripheral vasodilatation in a normal subject is a sharp increase in cardiac output As this does not occur with the faint, one must postulate cardiac inhibition as a factor in the dynamics of the faint If the heart increased its output in a normal fashion, the observed fall in peripheral resistance would not produce a striking fall in arterial pressure

The radiologists say the heart gets big This fits all right with the presence of a fall in arterial pressure, and would seem again to point to the fact that there is a cardiac element

Sharpey-Schafer In a bradycardia wouldn't you expect the heart to get bigger?

Stead Not to this degree of dilatation

Fremont-Smith It seems to me that, in the experiments where the faint was preceded by bleeding, you have a reduced blood volume, there is very good reason to expect an inadequate return

of blood to the heart, and, therefore, with the sudden muscular dilatation, you would expect a drop in cardiac output because the heart hasn't the return blood to call upon

Stead I think you could expect it if we did not believe that the faint is not necessarily associated with marked lowering of the atrial pressure

Fremont-Smith Haven't the people who faint without blood loss already had a preliminary fall in blood pressure?

Sharpey-Schafer I think that the people who faint spontaneously get a dilatation somewhere else, possibly in the splanchnic area.

Fremont-Smith A preliminary one, and then a secondary muscular dilatation?

Sharpey-Schafer What we have observed is this if you take a normal subject and make him feel sick, there is a sharp drop in the auricular pressure, and this may be followed by fainting

Moore Doesn't that also make you think of vagal effects and bradycardia and the picture you get in overdoses of cholinergic drugs and so on, which are syncope-like in nature

Sharpey-Schafer I think that whatever the method used to lower blood pressure acutely in unanesthetized man, bradycardia may result

Moore I wonder if that doesn't antedate the faint

Burton Is the bradycardia prevented by atropine?

Howarth After the administration of atropine to a postural fainter, it is still possible by the same postural change to produce loss of consciousness and a fall in blood pressure from muscle vasodilatation, without any change in heart rate The bradycardia is abolished

Bradley Fainting may be rapidly induced by the following maneuver (*a*) the abdominal pressure is raised for several minutes in recumbency by means of a wide pressurized abdominal binder or corset, (*b*) the patient is tilted into the upright position, and the abdominal compression is released I regard this phenomenon as evidence for primacy of a change in the cardiac output in the pathogenesis of syncope, because it seems reasonable to suppose that release of the abdominal binder would open up a large venous bed in which blood would accumulate and fail to return to the heart

Nickerson After that period of stasis, isn't it possible that the vascular beds in question are very markedly dilated?

Bradley I agree that the venous occlusion induced by the binder would operate to produce arteriolar dilatation and resultant "reactive hyperemia," but this process would take place during com-

tion to account for the fall in blood pressure

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of blood to the heart, and, therefore, with the sudden muscular dilatation, you would expect a drop in cardiac output because the heart hasn't the return blood to call upon

Stead. I think you could expect it if we did not believe that the faint is not necessarily associated with marked lowering of the atrial pressure

Fremont-Smith: Haven't the people who faint without blood loss already had a preliminary fall in blood pressure?

Sharpey-Schafer I think that the people who faint spontaneously get a dilatation somewhere else, possibly in the splanchnic area.

Fremont-Smith: A preliminary one, and then a secondary muscular dilatation?

Sharpey-Schafer. What we have observed is this: if you take a normal subject and make him feel sick, there is a sharp drop in the auricular pressure, and this may be followed by fainting.

Moore Doesn't that also make you think of vagal effects and bradycardia and the picture you get in overdoses of cholinergic drugs and so on, which are syncope-like in nature.

Sharpey-Schafer: I think that whatever the method used to lower blood pressure acutely in unanesthetized man, bradycardia may result

Moore I wonder if that doesn't antedate the faint

Burton. Is the bradycardia prevented by atropine?

Howarth: After the administration of atropine to a postural fainter, it is still possible by the same postural change to produce loss of consciousness and a fall in blood pressure from muscle vasodilatation, without any change in heart rate The bradycardia is abolished

Bradley: Fainting may be rapidly induced by the following maneuver. (*a*) the abdominal pressure is raised for several minutes in recumbency by means of a wide pressurized abdominal binder or corset, (*b*) the patient is tilted into the upright position, and the abdominal compression is released I regard this phenomenon as evidence for primacy of a change in the cardiac output in the pathogenesis of syncope, because it seems reasonable to suppose that release of the abdominal binder would open up a large venous bed in which blood would accumulate and fail to return to the heart

Nickerson: After that period of stasis, isn't it possible that the vascular beds in question are very markedly dilated?

Bradley I agree that the venous occlusion induced by the binder would operate to produce arteriolar dilatation and resultant "reactive hyperemia," but this process would take place during com-

tion to account for the fall in blood pressure.

Burton: The skin is quite constricted all through, very pale

Sharpey-Schafer. Yes There is probably actual constriction in the skin.

Bradley You feel sufficiently secure in the cardiac output data to say that cardiac output does not drop at all?

Sharpey-Schafer I think it does drop

SEQUENCE OF EVENTS ACCOMPANYING FAINTING

Bradley. Which comes first, the fall in the cardiac output, the decreased resistance, or syncope?

Sharpey-Schafer The sequence of events is fall in cardiac output, then suddenly muscle vasodilatation, the exact timing of the bradycardia and the muscle vasodilatation have not as yet been established It is a question of continuous records, the difficulty being that it takes a second or so to measure any blood flow, because you have to put on a collecting cuff and measure the rate of volume increase

Bradley You think it is possible, then, that the blood pressure falls initially with syncope because the cardiac output suddenly falls?

Sharpey-Schafer There is usually some fall in blood pressure as the person bleeds It is not usually very great The great fall in blood pressure occurs with the muscle vasodilatation

Stead There is a striking fall in peripheral resistance and much less change, if any, in cardiac output At first glance, then, one says that the reaction of the heart is not important in the faint However, one of the most striking effects of peripheral vasodilatation in a normal subject is a sharp increase in cardiac output As this does not occur with the faint, one must postulate cardiac inhibition as a factor in the dynamics of the faint If the heart increased its output in a normal fashion, the observed fall in peripheral resistance would not produce a striking fall in arterial pressure

The radiologists say the heart gets big This fits all right with the presence of a fall in arterial pressure, and would seem again to point to the fact that there is a cardiac element

Sharpey-Schafer In a bradycardia wouldn't you expect the heart to get bigger?

Stead Not to this degree of dilatation

Fremont-Smith. It seems to me that, in the experiments where the faint was preceded by bleeding, you have a reduced blood volume, there is very good reason to expect an inadequate return

is liable to stop breathing If this occurs, then an asphyxial bradycardia may follow, and this type of bradycardia is unassociated with changes in blood pressure This second type is presumably the bradycardia reported by Mathieson in 1910, and it occurs after vagotomy and in the anesthetized animal

Nickerson If you prevent the bradycardia with atropine, do you also prevent the loss of consciousness?

Howarth It is very difficult to be certain when a rabbit loses consciousness All I can say is that after being suspended for a certain time, the head falls forward and the heart slows Then, if the head is allowed to remain there, the animal generally gives a twitch and a kick, the heart speeds up again, and the head is raised

Nickerson The whole sequence of events is abolished by the atropine?

Howarth. As far as one can tell at the moment

Hyman Coming back to this business of having a chap exercise his lower limbs and putting arterial occlusion cuffs on them and holding them on for ten minutes or so and releasing the cuffs, the rate at which the cuffs are released will determine pretty much whether he will faint If you take off the cuffs the way you take your belt off, he will pass out every time, but if you deflate the cuffs rather slowly, then you stand a good chance of getting him back It seems to me when you deflate the cuffs slowly, you still have the same amount of pooling in the legs, don't you? But it would eliminate the thing that Dr. Stead is talking about

Stead If you take a normal person and have him lie flat, then suddenly throw him into the upright position, you have a rapid drop in pressure, which then returns approximately to the resting level He very frequently feels giddy The mean arterial blood pressure in his foot when he is horizontal is around 100 mm Hg On standing, the mean pressure in the feet is around 210 mm Hg, which is pretty good hypertension In the head, subtracting the weight of the column of blood from the pressure derived from the heart, instead of having a mean pressure of 100, he will have a mean pressure of, say, 85

The blood flow into the foot is instantaneously increased upon tilting upright because of the marked rise in mean arterial pressure This rapid flow is of rather short duration during motionless standing, because the arterial pressure is opposed in due time by a column of blood in the venous system, extending from the foot to the heart Thus, there is a period of time in which giddiness occurs when it

pression and would not be affected by it The pressure imposed by the binder amounts only to about 20 mm Hg, which is insufficient to change arterial pressure in any way and it does not therefore impede arterial inflow except insofar as increased venous pressure changes the gradient across the vascular bed Any effect due to reactive hyperemia should be acting throughout the control period

Sharpey-Schafer. You have never measured what is happening in the muscle?

Bradley No

Burton Would you think it is possible that the discharge of the pituitary which takes place in a faint could possibly be primary, or do you regard it purely as secondary?

Sharpey-Schafer I should have thought it was secondary For example, if you do other tricks which are not necessarily associated with muscle vasodilatation, such as the Valsalva maneuver, or if you bleed a patient a little bit and then do a Valsalva, so that you get the blood pressure, the filling pressure, and the cardiac output low enough, then you may precipitate the faint of muscle vasodilatation, and the faint may last for quite a long time

Burton Pitressin doesn't really imitate this picture at all, does it?

Sharpey-Schafer No

Howarth The hutch rabbit held up by the ears is the classical textbook example of fainting in animals And certainly if you suspend a hutch rabbit in the vertical position, it appears to lose consciousness, and its heart slows The heart rate may fall to 70 per minute, and electrocardiograms show that this is a sinus bradycardia Continuous intra-arterial pressure records taken at the same time show that the bradycardia is not necessarily associated with a fall in blood pressure In fact, the blood pressure may remain unchanged in some cases at a normal level The animal keeps on breathing throughout It may then give a twitch or a kick, the heart rate increases rapidly to its previous level, and the rabbit appears to regain consciousness The bradycardia can be abolished immediately by snipping the vagi, and within a few seconds by the intravenous injection of atropine or of anesthetics such as Nembutal or Pentothal

Nickerson Does atropine prevent the fainting as well as the bradycardia?

Howarth The bradycardia does not occur afterward if the animal is kept in the erect posture, at least this type of bradycardia appears to be abolished But the suspended rabbit is a frail creature and it

Moore It is as though we are talking about the blood vessels being always full of blood The valves are flexible, and they transmit pressure in reverse direction perfectly well

Burch Not immediately, if they function adequately

Haley You exercise the foot a little bit and the pressure will drop down to 35, and it takes a while before the pressure rises sufficiently again to push the blood back to the heart

Stead Dr Remington feels that the reserve blood is stored in the heart We do, too, when pushed in a corner If you take people who have been sympathectomized, stand them up and let the blood pressure get quite low, and measure the blood flow in their hands, you will find it is appreciably reduced, but if you measure the over-all cardiac output with a systolic pressure in the neighborhood of 60 or 70, you may find there is no reduction at all in the cardiac output The simplest interpretation of this would be that blood comes out of the heart, and, as Dr Burch just said, it has two ways to go It is going to go to the area in which you have the greatest effective pressure head and most dilated vessels, and I think the only explanation is that in certain situations the circulation in the lower half of the body goes up as the circulation in the upper half of the body goes down

Burton In the normal person it takes only about three seconds for the vasoconstrictor reflex to come on in the feet when he stands up Right away the vessels constrict

Burch You are actually measuring the rate of swelling of the legs and not forward flow

Stead Only blood can be getting into the foot

Burch But how much of that is venous in origin?

Stead Back flow through the veins can be excluded by placing an occluding venous cuff about the ankle, inflated to a pressure sufficient to exceed the venous pressure produced by gravity but not high enough to collapse the artery and interfere with arterial inflow

I can state my side of the argument very easily I think that in these reflex faints, a strong element of cardiac inhibition not related to the filling pressure of the heart is an essential part of the picture

Haley Would you care to speculate whether you might be having a modification of the Bainbridge reflex?

Sharpey-Schafer I am not very happy about the Bainbridge reflex in man It does not seem to work too well.

Haist What happens to cardiac output when a person is quietly put in a vertical position? I was under the impression that it went

is perfectly possible that the cardiac output is increased to a moderate degree. The arterial pressure in the head has fallen, and the flow down into the empty veins is considerably accentuated during this period of time If you measure only the things that have occurred in the outstretched arm or head, you would assume the cardiac output has fallen, but you at least know that in one area the blood is going fast There has to be actual measurement of the cardiac output on standing before one can be certain of what is happening

Moore Aren't you saying that the flow is fast because the blood pressure in that leg is 210?

Stead That is very easy to measure If the veins of the foot are empty when horizontal, the rate of swelling of the foot when the subject is first tilted gives a measure of the foot flow

Moore But that doesn't mean flow through

Stead. Flow through into the veins until the foot is full

Moore The normal human being does not faint every time he stands up, unlike the paraplegic who is pulled to a standing position The normal person reduces the peripheral flow into the foot and, despite a higher venous pressure, the flow is less When a normal person is kept standing for so long a time that the nervous element gets tired out, then he has a typical hypotension and may die This is crucifixion

Stead I suggest that during the first fifteen to thirty seconds of standing, the situation may be different from what occurs later

Bradley· During the first seven beats, the arterial pressure changes in accord with the hydrostatic shift, but then a reflex mechanism of some kind takes over The pulse speeds up, and there is a rise in the blood pressure which can be attributed to generalized vasoconstriction because it has been found that the cardiac output decreases in the upright position (9)

Stead This has nothing to do with his fainting reaction It is possible for him to faint in the first five or ten seconds after he stands up At the time, his cardiac output may actually be high

Haley. There is data on the rate of rise of the venous pressure and of the arterial pressure That would be the clue to how long it takes the blood to get back to the heart

Moore There is good data on that

Haley· During the first six seconds, the pressure may be quite low in the dorsum of the foot

Moore· How can it be unless you think the veins are empty?

Haley They are

Stead Standing, or leaning against a wall, causes a marked reduction in cardiac output, which may go to the point of fainting But I maintain that when something acute is done, like letting off the abdominal pressure, you can come to no conclusion as to what happens to the flow in the lower part of the body from observations on the pressure in the arms

Sharpey-Schafer I should like to say one other thing I do think there must be a distinction made between an acute fall of blood pressure in brain vessels causing unconsciousenss, due to many different causes of which the Valsalva is one, and the phenomenon of muscle vasodilatation There are a number of different syndromes and different mechanisms

Haley Did you take any records of pulse pressures as the subjects went into the bradycardia and faint?

Sharpey-Schafer Yes, they are very small

Haley Their smallness would suggest a decreased output

Sharpey-Schafer As the bradycardia comes on, pulse pressure increases

DELAYED HYPERKINETIC REACTIONS FOLLOWING PROLONGED OR SEVERE BLOOD LOSS

There is one more point I should like to make about hemorrhage in man Most of the cases that one sees in hemorrhagic shock in civil life are cases of gastrointestinal hemorrhage When the patients were seen in a state of low blood pressure, we were surprised to find in many cases that cardiac output was not much reduced and might even be increased So far as we could tell, the venous pressure was low If you raise the venous pressure with transfusions, the cardiac output goes up to quite a high level, and at that stage the blood pressure recovers (10)

We have been able to make consecutive measurements of cardiac output on normal men for a considerable period after fairly large venesections The subject in Figure 9 was bled 600 ml He had little or no fall in blood pressure and a slight acceleration of the heart He did not faint Cardiac output dropped following the venesection It remained low for perhaps two hours or more, and then there was a change At about four hours, the output was considerably higher than it was in the control period The heart rate during this period did not change much The venous pressure was decreased, of course, by venesection, but in four hours the venous pressure had risen

We had thought originally that perhaps we could explain the rise in cardiac output mainly by the slight increase in heart rate

down about 20 to 25 per cent

Sharpey-Schafer Yes

Remington Aren't we really quarreling over a question of time? Do you mean in the first two beats, or by the time a blood determination can be done? If it is in those first few beats and if we can still speak about cardiac output, I think it ought to go up

Burton Normally, it goes down, but Bazett found that in a man acclimatized to heat, it does not It may even rise slightly between lying and standing It is hard indeed to explain

Remington Once again, of course, we are talking about measuring the cardiac output when we can get to it

Bradley Of course you can't measure those two beats in man

Remington We can measure those two beats in the dog, and we find that the cardiac output goes up.

Bradley A dog isn't a man, and I think that is an essential point It is very difficult to transfer to man the findings in dogs

Remington Can't we answer it this way. watch the heart in the first few beats Does the heart decrease in size or stay the same?

Stead I am reporting this secondhand, but I have been told that the heart gets bigger at the time the pressure is falling

Howarth It should get smaller before the onset of the bradycardia

Remington That is the bradycardia effect I was speaking about suddenly bringing the man upright

Sharpey-Schafer The heart gets smaller

Remington Then the cardiac output is up if it gets smaller

Stead Could I make a brief summary and see how much agreement there is on this? First, if you have an individual standing up with a low arterial pressure and a reduced forearm blood flow, no conclusion can be drawn as to the cardiac output. Second, in any acute alteration in which the venous system has become empty and is allowed to refill rapidly, there may be a fall in arterial pressure which does not necessarily indicate a fall in cardiac output This is particularly important when, because of gravity, there are marked differences in the mean arterial pressure in different parts of the body There may be a redistribution in the amount going up to the arms and head and the amount going down, and under those circumstances, at the time a patient is losing consciousness, the actual minute output or stroke output may be increased, with most of the blood perfusing the empty part of the body

Bradley. The redistribution has already taken place This is something that happens acutely on assumption of the upright position

adrenalin is administered

Sharpey-Schafer That is not my idea of it It is a phenomenon which may go on for a very long time, under suitable conditions for weeks

Moore Which phase do you refer to – the low cardiac output phase or the high?

Sharpey-Schafer The high cardiac output phase

Fremont-Smith Wouldn't adrenalin do this same thing, although not lasting as long?

Sharpey-Schafer The cardiac output can be increased and very little change in blood pressure produced If the dose is exactly right, there is hardly any change in heart rate either.

Nickerson: If these changes are due to epinephrine, is it not surprising that the change in heart rate and the change in cardiac output are so separated in time? The former occurs almost immediately and might well be an epinephrine effect, while the change in cardiac output develops much later

Sharpey-Schafer. Yes My own impression is that the time taken to develop the hyperkinetic syndrome is about three or four hours as a minimum, perhaps it is usually longer

Burton Recent work in our school on cardiac increase after hemorrhage has shown that high cardiac output is not prevented by bringing the volume up to what it was, but it is prevented if packed cells are put in In other words, it seems to be related somehow to the small carrying capacity of blood for oxygen, not to the decrease of volume, which is a very interesting result, I think

Sharpey-Schafer That is an obvious possibility, because, as you know, in severe anemia, with 30 per cent hemoglobin or less, cardiac output is nearly always raised considerably (11) One would think this was the same sort of phenomenon We have seen this occur at quite high hemoglobin levels The subject in Figure 9 might have a drop of, say, 10 per cent in hemoglobin in four hours I have also seen it occur in polycythemia bled from 150 per cent hemoglobin down to about 110 It is still quite true that there is a change in hemoglobin, and I presume that might be a precipitating factor

Moore The only trouble is that changes in hemoglobin level can be due to other forms of hemodilution where there is not necessarily the tachycardia I don't know about cardiac output measurements Also, it is a fact that that patient's hemoglobin, you say, is down 10 per cent, but after a bleeding of 600 ml , in three hours his cardiac output is going up, and the chances are his hematocrits are practically within the limits of error in that time

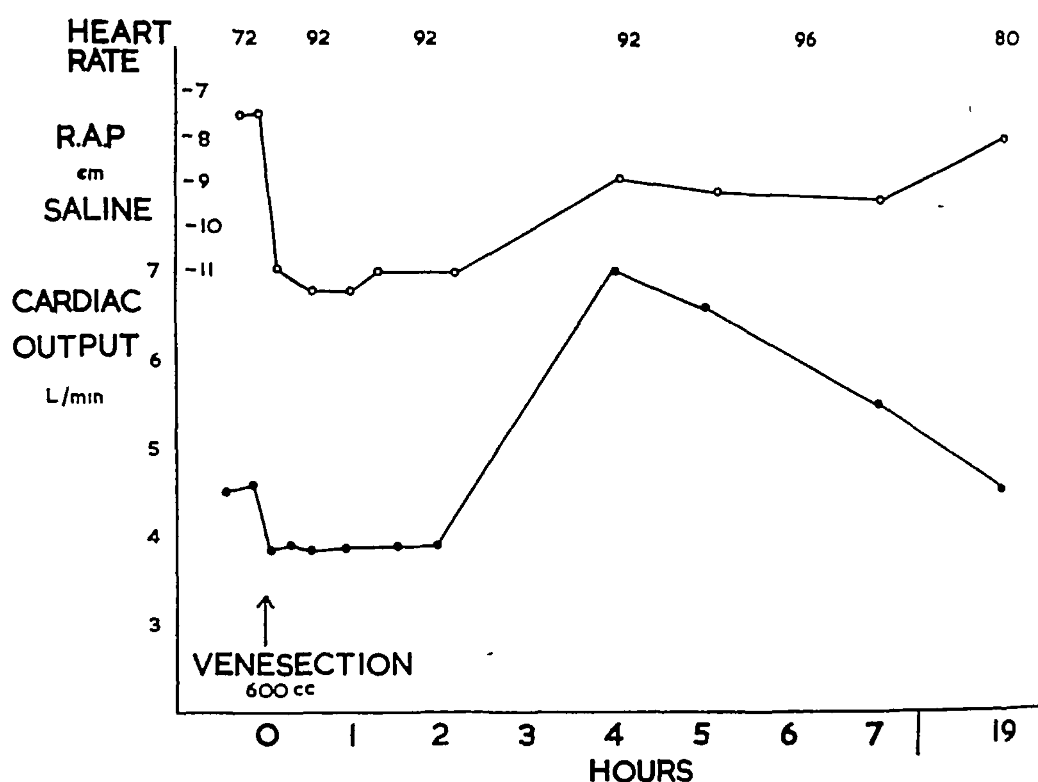


FIGURE 9 Serial cardiac output determinations in a subject bled 600 ml This subject did not faint Cardiac output rose above resting level at about 4 hours R A P right auricular pressure

plus the return of venous pressure to normal In this subject, cardiac output returned to the resting level after nineteen hours. We have venesected a considerable number of subjects, but we have never seen this hyperkinetic phase occur immediately after hemorrhage There is always a delay of some hours This phenomenon in dogs has been described by Harrison in similar experiments The mechanism is uncertain I don't know whether Dr. Shorr or Dr Zweifach can help us, it seems to me that a nervous mechanism is an unlikely cause of the hyperkinetic state Most of the clinical cases of gastro-intestinal hemorrhage that one sees have reached this hyperkinetic phase, and if they bleed again, the general level of output is not as low as might be expected

Fremont-Smith With the exception of the reduction in blood volume that was presumably due to hemorrhage, aren't your results similar to the aftereffects of a moderate dose of adrenalin in man? There, too, one finds increased circulation rate, increased venous blood pressure, increased cardiac output, and, if anything, a fall in diastolic blood pressure, and perhaps a normal or even small fall in systolic blood pressure The heart rate is also increased after

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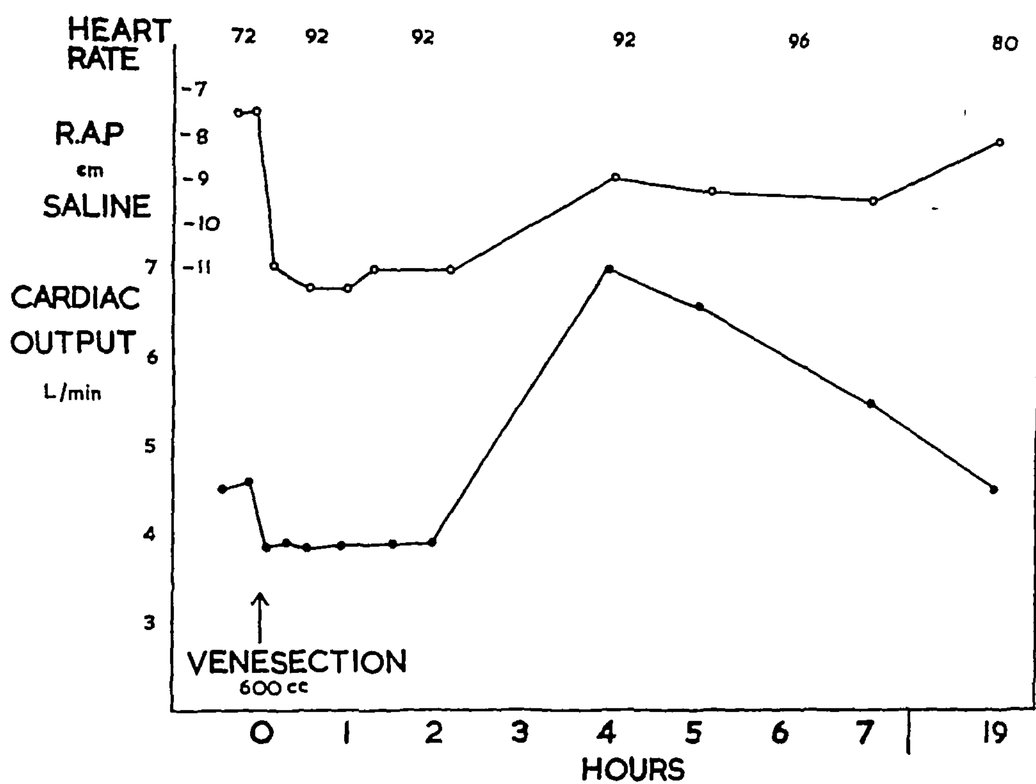


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change in pulse rate, shutting off a large fistula may not. The sensitivity of the autonomic nervous system to the stimulus seems more important than the size of the stimulus It would appear that the behavior of the pulse is a function of how the autonomic nervous system is rigged up and that the circulation can be altered within fairly wide limits without changing pulse rate

Burch. In Figure 9, how do you think the blood returned to the heart to maintain the cardiac output at such a high level without very much change in venous pressure? Was thoracic pressure decreased? Was breathing deep, with an increase in the effective intra-auricular pressure?

Sharpey-Schafer There is a rise in that time in venous pressure

Moore The venous pressure and venous flow are certainly very different things

Burch They are I just wondered about the mechanism of the increase in volume flow to the heart After all, the blood is leaving the heart and therefore must be returning into it at a rapid rate.

Sharpey-Schafer Isn't the venous return the same as the cardiac output? The venous pressure is quite different It is tempting to think that some change has occurred in the capacity of the venous system, because, in fact, at this point the blood volume seems to be less than it was originally and yet there has been some recovery of filling pressure of the heart One would imagine that might come about by a small increase in venous return In fact, if you look at people who have been bled, very often you will find that the visible veins are small, yet the blood flow in the forearm or hand is normal, or, if anything, a little up

Burch The sum of the flow into all the parts must show an increase, since the cardiac output is increased

Sharpey-Schafer It might be going somewhere else

Stead How do you visualize the heart filling under those circumstances?

Sharpey-Schafer I think you have venous pressure coming back toward normal and an increased rate Another factor may be affecting the heart itself It is more efficient

Burch Do I dare mention adrenalin at this point?

Sharpey-Schafer I don't think it is adrenalin

Fremont-Smith Adrenalin would increase the efficiency of the heart, wouldn't it?

Sharpey-Schafer Yes

Moore I think it is important to mention here that you get exactly the reverse situation, at least with respect to heart rate, in a sick

Sharpey-Schafer: As you know, the rate of dilution after such bleedings in man is an extraordinarily variable thing and may be very long, it may take forty-eight hours or more to dilute out

Moore That is what I mean Actually, the oxygen-carrying capacity per milliliter of that patient's blood at three hours is probably just about what it was to begin with

Sharpey-Schafer That is what I think, too I am not happy about that explanation

Remington What about the oxygen consumption?

Sharpey-Schafer The oxygen consumption has not varied much during this time

Green Is there any data on the venous oxygen tension during this period between the low and the high?

Sharpey-Schafer No, we have not measured that

Burton In dogs, it was not changed very much

Moore: Have you done any measurements of respiratory rates or blood pH in these?

Sharpey-Schafer No Looking at the subjects, it would not be thought there was any increase in respiratory rate

Haist Does that increase in heart rate help in compensating for reduced venous return?

Sharpey-Schafer It is a very difficult question I presume it does, but what the mechanism is, I don't believe we know

Haist It apparently does have some compensatory effect because if the rate is diminished at that point the blood pressure falls

Nickerson Could part of this reaction be in the reverse direction, that is, could the increased cardiac rate be responsible, in part, for the reduced venous pressure?

Sharpey-Schafer No If you bleed a lot of men, you will find some maintain their rate at exactly the same level, and if you take enough blood out, you will reduce the venous pressure

Nickerson Does it require a greater withdrawal of blood to reduce the venous pressure in these cases than in those which respond with a good cardioacceleration?

Sharpey-Schafer From an absolute change in venous pressure? I don't think we could say very much about that

Stead Some observations on an A-V fistula may help in understanding the variation in human pulse rate A graded variety of A-V fistula from very big ones to very little ones can be taken On occluding the fistula, the pulse slows There is no relationship between how big the A-V fistula is and how much the pulse slows Shutting off a rather small fistula may produce a very dramatic

change in pulse rate, shutting off a large fistula may not The sensitivity of the autonomic nervous system to the stimulus seems more important than the size of the stimulus It would appear that the behavior of the pulse is a function of how the autonomic nervous system is rigged up and that the circulation can be altered within fairly wide limits without changing pulse rate

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patient with a much higher take-off point, say at 120 In other words, the pulse rate goes up to 140 or 160, diastolic filling time and the stroke volume go far down, cardiac output goes down, and the patient goes into severe hypotension because of tachycardia The most striking example of that, of course, is in a patient with mitral stenosis, where there is actually a block to diastolic filling This response, which you might think of teleologically as protective, can become deleterious if the take-off point is higher

Sharpey-Schafer Yes, I think you can do that and start bleeding from a high level

Remington I am unhappy about this sequence of events in which the heart accelerates and, therefore, the cardiac output goes down – let's say it went down despite the fact that the heart accelerated An increase in heart rate per se to the level that you spoke of, 160, with venous return the same, should not decrease the cardiac output, but rather increase it

Moore I say that the critical level is somewhere between 140 and 160, and above that rate the human heart is, so to speak, spinning its wheels, because diastolic filling time is so short that the stroke volume goes far down and cardiac output falls

Remington If you said 180 .

Moore I would agree, 180

Remington: A rate of 160 is too near the borderline

Moore In mitral stenosis, the same thing happens at 110, and it is spectacular Surgical mitral stenosis cases called our attention to this problem, and then, having had our eyes opened to that possibility, we found it in other patients, but with a much higher pulse rate I would put it definitely below 180

Burch Returning to the term "efficient," what do you mean by it?

Sharpey-Schafer I don't know I am not sure whether it can be explained on the basis of the heart rate plus venous pressure change Some other factor, like adrenalin, for example, may have to be included

Burch You didn't mean work efficiency?

Sharpey-Schafer No, I was using the wrong term As you transfuse and the venous pressure rises, the heart slows, the blood pressure goes up and the output reaches a high level

Moore That is a good example of what I was talking about

Sharpey-Schafer Many surgeons who see a hemoglobin of 22 per cent do not like to operate, but if they see one somewhat higher, they are prepared to carry on In many subjects under these conditions, however, if the hemoglobin is increased, the circulation

may not be altered for a long time afterward.

Moore: The circulation may not have changed very much, but something very important has been done with those 540 ml. of concentrated corpuscles, exactly that volume has been added to the vascular bed and it stays there, in sharp contradistinction to anything else, including whole blood.

Sharpey-Schafer: But my point is this: if the surgeon then does an operation during the hyperkinetic phase and bleeds the patient 500 ml., there may be a very difficult situation again.

Moore: Quite so, but not nearly as difficult a situation as if the surgeon had proceeded to bleed 500 ml. without the prior administration of red cells.

DELAYED RESPONSES RESEMBLING HEART FAILURE AFTER PROLONGED HEMORRHAGE

Sharpey-Schafer. There is another phase, a curious phase which we have seen uncommonly after hemorrhage. The point here is this: if bleeding goes on in small amounts for a long period, a state

TABLE IV

Data from a Patient with Severe Recurrent Gastrointestinal Bleeding

	B.P. mm. Hg	Pulse Rate	R.A.P. cm. saline	C.O. liters/min.	Hb %
4th Day	72/40	100	−6	4.0	59
	Transfusion 650 ml. Blood				
	92/72	104	−3.5	5.6	
11th Day	86/48	114	−2.5	8.5	40
	Transfusion 250 ml. Blood				
			0	8.6	
23rd Day	72/50	128	+12	7.9	32
	Digoxin mg. 1.5 i.v.				
	90/60	120	+7	8.7	

The days refer to the time after the bleeding commenced.
B.P. arterial blood pressure
R.A.P. right auricular pressure
C.O. cardiac output
Hb hemoglobin concentration in per cent of normal

of affairs arises which appears to be heart failure. For example, on the twenty-third day, in Table IV, the blood pressure is still low. The venous pressure at this point is considerably raised, the cardiac output is still high, hemoglobin is low. This, I would suggest, is the same sort of picture as is seen in severe anemia. If one finds the blood pressure low in this phase and one knows the subject has bled, one may think that something must be done to raise the blood pressure at all costs. Transfusion is then given on top of the high venous pressure, and the next thing that happens is that the subject becomes breathless, the blood pressure rises, there is intense peripheral constriction, pulmonary edema appears, and the patient may die. If you look through the deaths from transfusion and deaths following hemorrhage, you will find quite a number in which this has occurred. So this is a late low blood pressure phase in man after hemorrhage in which the venous pressure is high, the output is usually somewhat up, and the hemoglobin usually low. This may persist for a long time.

Zweifach: Isn't there a great deal more wrong with that individual than merely a low blood pressure for twenty-three days? Haven't other things happened in the meantime?

Sharpey-Schafer: Yes.

Moore: If that were a young adult with gastrointestinal bleeding, the rest of the picture would be pretty important.

Sharpey-Schafer: The patient is not very old although it is much commoner in older people, we have seen it in young adults.

Moore: We should also be aware that that patient could have quite normal blood volume with that particular situation, and if he was given another 500 to 700 ml. of blood, he could be tipped over because he is already compensated.

Sharpey-Schafer: The other important factor is that he already has high venous pressure, and if it is pushed up further, it is like taking a case of congestive heart failure and giving a transfusion.

Fremont-Smith: The patient had generalized edema?

Sharpey-Schafer: He had edema.

Moore: Isn't it a fact his venous pressure went back and his blood pressure went up with Digoxin? Isn't it pretty well known as to what is affecting him?

Burton: We shouldn't forget the purely physical factor that with a hemoglobin of 32 per cent, viscosity of the blood is only about half of normal, that is a very real factor in lowering peripheral resistance. If the geometry of the bed is just normal, resistance would be half normal.

Sharpey-Schafer. But it is uncommon to get such blood pressures at this level of hemoglobin in straight anemia

Shorr. Is the skin warm?

Sharpey-Schafer Yes If such patients have an attack of breathlessness — and it is easy to produce breathlessness by just laying them flat — their skin goes cold, they become constricted

Stead Do you think he had heart failure or not?

Sharpey-Schafer It depends on how you define heart failure It is really a clinical, and not a scientific, term But I would say this patient had heart failure

Burch If you had to speculate, what would you think his pulmonary pressure was?

Sharpey-Schafer Possibly increased

Stead Did you have the vital capacity?

Sharpey-Schafer It may be moderately reduced

Burton Would it help him if you gave him a short venesection?

Sharpey-Schafer We have done that We have had cases of severe anemia in this state that we have venesected to save their lives

Moore Don't you rather shy away from the term "anemia" for a person like that? Such a person probably has perfectly normal blood volume, there is just a low cell content His red cell concentration is down but his blood volume may be normal The fact that his venous pressure is up, that his blood pressure goes up when his pulse rate goes down, and the response to Digoxin suggests to me that he has a perfectly normal blood volume but that his heart is not dealing with the venous return that is being presented to it I agree with Dr Stead that it is heart failure

Nickerson Do you feel that one has to have a reduced blood volume to have anemia?

Moore That is purely a question of semantics I think if we use the term "anemia" for a normal blood volume at a low red count hematocrit or hemoglobin, it is all right

The patient under discussion has an elevated venous pressure and rapid pulse, and when his pulse comes down, his venous pressure goes down and his blood pressure goes up

Sharpey-Schafer If you raise the venous pressure by means of a rapid transfusion, his cardiac output will almost certainly go down

Fremont-Smith You also have to take into consideration what happens between the eleventh and twenty-third days, because this was a period when his venous pressure was normal, and then it went up It seems to me that during this period there is an accumu-

lation of blood on the right side, and hence the heart is progressively failing to deal with the blood that is brought to it, regardless of the measured output at any given point. For example, his cardiac output dropped from 8 6 to 7.9, and his venous pressure was raised from –0 to 12

Green What happened to his venous oxygen at the point when he had the high venous pressure?

Sharpey-Schafer· We don't know the actual oxygen tension

Green· I have asked two or three times about the venous oxygen The reason is, Dr. Little (12) in our school looked up a lot of data on venous pressure and the one thing he found to correlate with it was the venous oxygen tension, suggesting there might be some sort of venomotor mechanism coming in and regulated by the venous oxygen tension, the relationship was more closely allied with the venous oxygen tension than with venous oxygen content.

Fremont-Smith Here we have a relatively simple situation, with quite a lot of facts about it, and a group of people who are thoroughly experienced in this field I think it is significant that we cannot agree on what is probably taking place between the eleventh and twenty-third days That in itself should give us pause

Moore We would have to know the rest of the clinical case to be able to reconstruct that

Fremont-Smith. It is the hydrodynamics we can't agree on

Burton: The increase in cardiac output in chronic anemia remains a complete mystery It is the most puzzling thing It will occur after acute hemorrhage, as well as after chronic hemorrhage or chronic anemia, won't it?

Sharpey-Schafer: Yes

Burton Would you agree that the experiments on the increase of cardiac output indicate that there is a long time factor, which is strongly suggestive of some hormone influence that we do not know about yet?

Sharpey-Schafer I should think so

Burton That is what I should have thought, but we do not know which hormone it is

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THE INFECTIOUS ELEMENT IN SHOCK*

JACOB FINE
Department of Surgery
Harvard Medical School

As a result of the previous discussions, I have discarded much of the paper I originally intended to present and will use only some notes compiled hurriedly If my remarks seem scattered, I ask your indulgence

By "shock" I mean a state of persisting deficiency of flow in the peripheral vascular system, however produced, manifested in man and animals by low blood pressure, cold, moist skin, pallor of skin and mucous membranes, and oliguria or anuria. These are the constant features of the syndrome I shall not deal with the inconstant ones, such as thirst, state of consciousness, and reactivity to pain The organism may recover from shock spontaneously or in response to therapy, in which case the condition may be said to be reversible Or the organism may fail to respond to all forms of therapy, in which case the shock may be termed irreversible

In the pre-antibiotic era, a familiar form of irreversible shock was seen frequently in overwhelming sepsis When a specific antidote for the infecting agent was found, this irreversible form of shock became reversible The same was true for shock due to massive hemorrhage until properly matched blood or satisfactory blood substitutes in adequate quantity became available Today, most patients with massive hemorrhage respond to adequate replacement therapy, even if shock has persisted for many hours There are, however, a few who do not survive prolonged shock from continuing hemorrhage in spite of the fact that at the time of death the blood volume deficiency has been largely or entirely corrected The problem is to discover what factor in these excep-

* The work here reported, and much more upon which it is based, has been supported in large part by grants from OSRD during the years 1941-45, by subsequent grants from ONR during the years 1946-49, and since then by the USPHS, in contracts between these agencies and Harvard University Additional support, related to the work with antibiotics, has been provided by the Lederle Corporation
The main thesis in this report is based on recent work in which the following men participated Drs Howard A Frank, Fritz B Schweinburg, Stanley Jacob, Harold Weizel, and Theodore Gordon

tional cases accounts for the irreversibility, i e, the failure to respond to transfusion The shock due to massive tissue injury or crush injury and to burns is also a form that sometimes fails to yield to adequate volume replacement therapy But it is not always clear whether the death, if it occurs while such patients are in shock, is due to unrelieved oligemia, to poisons of tissue origin, to pathogens, or to distortions in metabolism or electrolyte balance that available methods cannot identify or correct

Thus, the phenomena of irreversible shock in man are encountered chiefly in massive burns, in some cases of massive tissue injury, in a few patients with prolonged shock from hemorrhage, and in some types of infection for which we have no effective antibiotic Familiar reversible forms of shock are those due to dehydration, to diabetic acidosis, and to simple, uncomplicated hemorrhage treated promptly and adequately

Many of the questions involved in an understanding of irreversible shock cannot be studied in man, and so we necessarily use the experimental animal In both man and animal, two types of irreversibility can be distinguished that which is reversible in its early stages and later becomes irreversible, and that which is irreversible from the beginning Let us take hemorrhagic shock as the simplest form of the first variety If we are to study this disorder in the experimental animal, it should best be done with as few complicating conditions as possible It is surprising how rare are the studies which have successfully avoided introducing factors which necessarily obscure the data that can be regarded as unequivocally derived from the loss of blood volume alone This is not easily achieved because of the necessity of making the essential observations The least we can do, it seems, in order to get the minimum data required, is to forcibly immobilize the animal, make incisions under procaine, and cannulate vessels Some of us add to these apparently innocuous procedures the use of heparin, some use barbiturates or other anesthetics Occasionally, we complicate the matter by doing major surgical procedures Few of us take sufficient account of the degree of malnutrition, environmental temperature, the not infrequent presence of fever in the animal, and so forth

In the last two years we have conducted experiments in an air-conditioned laboratory with a steady and comfortable room temperature We have used only apparently vigorous and well-nourished animals, free of fever, and, except for a small dose of morphine given an hour before starting the withdrawal of blood, have used

no sedatives or anesthetics In recent months we have even avoided morphine

TECHNIQUE FOR INDUCING SHOCK

After cannulating the groin vessels of a dog under procaine, blood is allowed to escape from the femoral artery into a reservoir containing a minimal amount of heparin The reservoir is elevated so that bleeding stops when the blood pressure has fallen to 30 mm Hg The blood lost into it reaches a maximum in a period of somewhat under an hour Such an animal lies quietly for some hours, during which time he exhibits the classical features of shock At some point the animal begins to take back blood from the reservoir There follows a gradual decline of the level of the blood in the reservoir The remainder is rapidly transfused at a certain point, which is indicated in Figure 10 by a pressor response

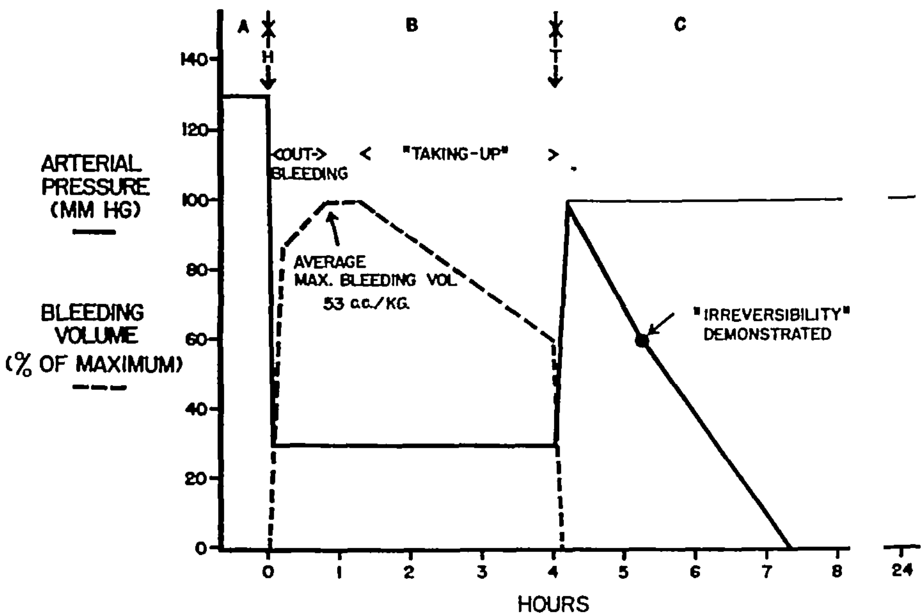


FIGURE 10 Reprinted, by permission, from Frank, H A, *et al* *Adrenal Cortical Therapy and Hepatic Vascular Resistance Two Aspects of an Inquiry into the Pathologic Physiology of Experimental Hemorrhagic Shock* Surgical Forum, American College of Surgeons, Philadelphia, W B Saunders Co, 1951 (p 522)

Zweifach: I should like to urge consideration of the fact that this type of experimental procedure, like any other experimental method used to study shock, has a number of inherent peculiarities which may limit the useful application of the data to other forms of shock In the first place, the animal is subjected to an abrupt, extensive loss of blood, and the blood pressure is rapidly brought down to 30 mm Hg This level of blood pressure could not be maintained by the animal for any protracted period of time, except

by virtue of being connected to a Lamson type, self-infusion reservoir Such a set-up permits the return of blood into the arterial system whenever sequestration occurs and the blood pressure begins to fall. By precipitating such a drastic hypotension, the circulation is curtailed immediately in all of the tissues of the body, and especially in the gut and the liver In fact, this is the type of experimental procedure which would exaggerate the gut factor On the other hand, when shock is produced by graded hemorrhage, several differences are apparent In the first place, an opportunity is afforded for a more adequate evaluation of compensatory mechanisms Secondly, the graded bleeding allows sufficient time for the redistribution of blood by whatever mechanisms the animal has available In these animals, the blood pressure stabilizes itself at a given level for a long period of time. Then the circulation begins to fail, either because compensatory mechanisms are no longer operative or because positive deleterious factors have been introduced Decompensatory changes may develop in a different sequence in such animals, and vascular collapse may be associated with changes in a variety of organ systems In the Lamson type of procedure, such changes are masked by the continuous reinfusion of blood from the blood reservoir, which serves to sustain the circulation arbitrarily until a given set of mechanisms undergo deterioration

Fine I prefer to impose a given load, which we can reproduce and which we know is exactly that load for the duration of the experiment As the graded hemorrhage technique is used, it is complicated by the presence of anesthesia

Zweifach The effects of anesthesia on the syndrome have been subjected to experimental study and have been found to have no specific effect on the sequence of changes, other than to accentuate decompensatory phenomena

Fine. I prefer not to use an anesthetic, believing that it further obscures the issue At the end of an experiment under anesthesia, it cannot be said that the animal has suffered a given degree of peripheral vascular collapse In order to put it in quantitative terms, it must be possible to say that this unanesthetized animal was subjected to a degree of shock in which his blood pressure was fixed uniformly at a level of 30 mm Hg I prefer to use this type of artificial set-up for purposes of making the observations upon which therapy can be judged

Zweifach It is possible that during shock a given organ system begins to undergo metabolic deterioration early in the syndrome With the Lamson type of procedure, this metabolic derangement

no sedatives or anesthetics In recent months we have even avoided morphine.

TECHNIQUE FOR INDUCING SHOCK

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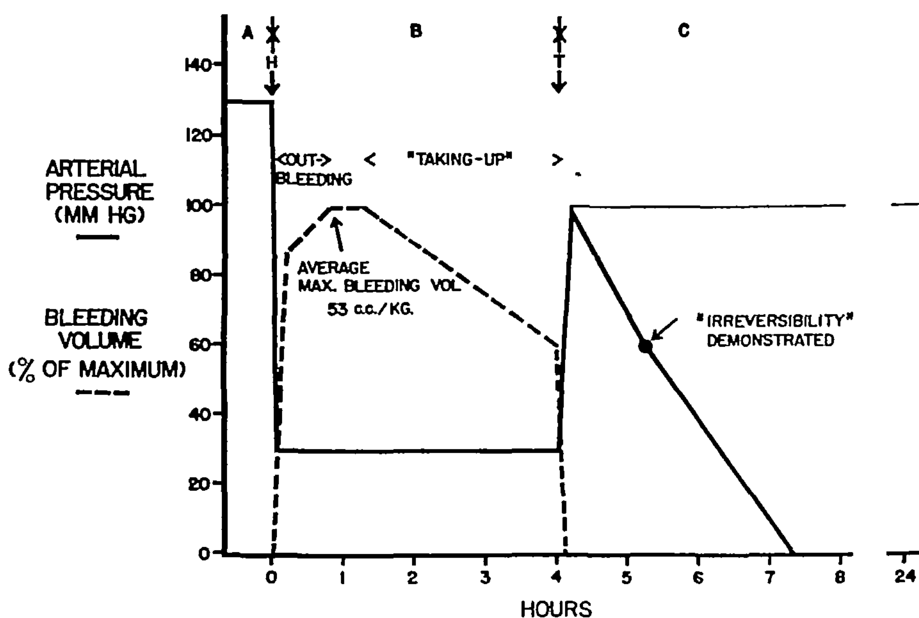


FIGURE 10 Reprinted, by permission, from Frank, H A, *et al* *Adrenal Cortical Therapy and Hepatic Vascular Resistance Two Aspects of an Inquiry into the Pathologic Physiology of Experimental Hemorrhagic Shock* Surgical Forum, American College of Surgeons, Philadelphia, W B Saunders Co, 1951 (p 522)

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wants to press that point as of possible therapeutic value because the effects of barbiturates are disastrous in a more important category The description you gave yesterday about what ether does to the circulation is a good example of what they do to the circulation The use of a barbiturate does not represent the situation as we know it clinically, for the patient does not go into shock with a barbiturate in him He is without it, presumably, when he sustains his injury And I prefer, for purposes of investigating this problem, to avoid the obscuration which results from the use of barbiturates or any other anesthesia

Zweifach I do not think that the use of anesthesia in shock necessarily complicates the experimental analysis of the syndrome There is no doubt that anesthesia aggravates the situation and that different anesthetic agents affect the end result in different ways The development of vasodepressor phenomena within the liver is not dependent upon the presence of anesthetic agents The relative period of hypotension required to bring about vascular decompensation is greater in the unanesthetized than in the anesthetized animal

Green When dealing with very low pressures, it is helpful to those of us interested in flow to know where the zero is

Fine Zero is the level of the heart

Green What is the level of the heart?

Fine Projected on the horizontal from the estimated level of the heart to the height of the bottle

Green Many of us use the carotid artery level, some use 5 cm anterior to the skin of the back, some use the dorsum as a level If I understand correctly, Dr Zweifach was criticizing the use of the Lamson bottle as being perhaps different from the Wiggers' technique. From my observation of the Wiggers' technique, it is necessary during the latter part, either the thirty or forty millimeter period, to add blood to keep the pressure from falling further Does it matter whether you add it with a syringe or use a Lamson bottle?

Zweifach I believe the major difference between the Wiggers' technique and Lamson's technique is the following the Wiggers' procedure permits the establishment of a degree of hypotension which the animal itself determines to be just compatible with survival This differs from animal to animal The blood pressure is kept at this level by giving small infusions (sometimes as little as 0 5 per cent of body weight) in order to prevent the abrupt collapse of the circulation In the Lamson type of procedure, the uptake of blood is considerable It represents 40 per cent of the total blood which is taken out into the reservoir This is necessary because the

is not permitted to develop because the animal begins to take up blood from the reservoir until an adequate perfusion of that organ is again possible This will occur progressively throughout the syndrome and to a varying degree in different tissues The Lamson technique, as employed by Dr Fine, arbitrarily sets up a given type of shock in which deterioration is allowed to develop to the point where the gut suffers vascular impairment and decompensation In such an animal, protection is afforded by factors such as Dibenamine or antibiotics which either prevent the gut from becoming hypoxic or in some way alter the vascular degeneration within that tissue I am trying to emphasize the fact that this is, in a way, a specialized form of shock and not necessarily representative of other forms of shock It is granted that gut hypoxia occurs in all types of shock, but perhaps not to the same extent as in the type of procedure which Dr Fine employs

Fine The objective of these experiments is to determine whether a given load of peripheral vascular deficiency of flow can be treated, and the result observed We are concerned not so much with what happens to a single organ, such as the kidney or the brain, as with the over-all result of a transfusion after a given load has been imposed upon the peripheral vascular system, that is, will the animal survive or die?

Zweifach I simply want to point out the dangers which exist when one tries to generalize from this type of experiment to experiments on animals subjected to hemorrhagic shock under pentobarbital anesthesia according to the technique of Wiggers In our experiments, an animal brought to the decompensatory phase of shock will die if given even a small dose of pentobarbital A comparable state of shock was set up with the use of the Lamson self-infusion reservoir, and several workers indicated (1) that the administration of pentobarbital during this stage was actually beneficial This occurred because the animal was able to receive a convenient infusion at this time from the blood reservoir connected to his arterial system

Fine In the first place, you and I have observed what happens to the peripheral flow when a barbiturate is given It distinctly aggravates the situation in the peripheral vascular system

Zweifach I am merely stating what other investigators have claimed, using the same procedure

Fine I think you are referring to Beecher's observations with respect to fluid lost into tissues (2) Barbiturate anesthesia seems to conserve fluid within the circulation I do not think Beecher

during shock, and each one has certain advantages for which the individual selects it, and each one, by virtue of the fact that it has advantages, also has limitations I think if we would specify quite clearly the advantages and the limitations, the goals and purposes, then there can be no conflict about the utilization.

Fine In Figure 10 the slope of the dotted line indicates the rate at which the dog is taking back the shed blood It demonstrates that compensatory vasoconstriction has failed and that peripheral vascular collapse has begun If compensation is not restored by this self-transfusion before some 40 per cent of the volume originally bled into the reservoir has returned to the animal, experience tells us that death will result in over 85 per cent of the animals, whether the remainder of the shed blood is allowed to run in by gravity or is forced in rapidly

A good pressor response will frequently follow the rapid infusion While this may be sustained for a variable interval, pressure declines When it has fallen to 60 mm or below, death follows quickly It is when the dog is in the stage of this decline in blood pressure, following transfusion, that we consider we are dealing with irreversible hemorrhagic shock Before the 40 per cent take-up has occurred, the shock is frequently reversible, that is, reinfusion of all the shed blood is usually sufficient to cure the shock and no other treatment is necessary We do not regard the shock as necessarily irreversible until the transfusions have been shown to be ineffective

This is our standardized form of experiment in hemorrhagic shock It is free of the harmful effects upon the peripheral vessels which barbiturates and other anesthetics impose, bringing about a continuous, evenly sustained, severe degree of hypotension which is not intensified or modified by drugs It determines irreversibility not in terms of a statistical prediction of average, expected results, but in terms of the dog's own circulatory state It demonstrates that irreversible hemorrhagic shock can be produced in dogs without the use of drugs

Since extensive study of the hemodynamic pathology of hemorrhagic shock by many investigators has failed to demonstrate an intravascular basis for the refractoriness to transfusion, the current of inquiry has shifted to a study of distorted tissue function resulting from hypoxia or anoxia as the possible core of the trouble The search appears to have excluded all vital organs except the liver Engel and his collaborators (3) have found distortions of intermediary metabolism which they attribute to disturbed liver func-

animal is arbitrarily maintained at a blood pressure which is below that usually encountered in the Wiggers' graded hemorrhage procedure

Burton We should remind ourselves that in our experiments on animals, which contain a great number of variables, all of us like to keep some factors as constant as possible It seems to me that at the present stage of our knowledge of this shock picture we have perfectly free choice One of us may choose to keep the blood pressure constant throughout the experiment, which is Dr Fine's choice Others may prefer to keep the volume of blood constant, which is very difficult to do, because even if none is added or taken away, there are fluid changes within the animal, with the result that the circulating blood volume is not constant I should think that the method is a matter of choice, and I should like to have us go on and hear what the results are in this particular case rather than discuss whether the particular variable chosen to be fixed is better than the ones we ourselves use

Zweifach I merely raise the point to indicate that this is not necessarily representative of what happens in other types of experimental shock

Burton I think we would all agree with that

Shorr As I understand the discussion, the question is not whether Dr. Fine is entitled to set up a standard set of conditions, but whether he is justified in saying that, under the conditions he has set, all of the reactions of the total organism to hemorrhage are preserved and the experiment therefore is an exact replica of what happens in shock

Selkurt Just one final question It would seem to be pertinent to find whether the bleeding volume remains constant

Fine· It does, but I shall give you the figures later on

Fremont-Smith I think this is a very interesting form of discussion I remember the opening meeting of our Conference on Blood Coagulation There were three methods of measurement for prothrombin time from three laboratories or three groups of individuals Each one's method was the best, and each had already attacked the others' methods publicly in the literature, each had written accusatory letters to the other Well, it took a morning to finally smoke out the fact that each method had its particular advantages with respect to goals As soon as both the goals and limitations were specified, there was no longer any argument about the method.

I think we have the same situation here We have two, three, five different methods of producing shock or of measuring an animal

strate that irreversibility to transfusion in hemorrhagic shock in the dog is due to bacterial action (Tables V and VI)

TABLE V

Experimental Hemorrhagic Shock
Effect of Antibiotics Administered Orally

Drug	Number of Dogs	Bleeding Volume (ml /kg)	Hypotension Period* (hrs)	"Taking-Up" Incomplete at 8 Hours	Survivors
None	185	53	4 8	12 (6%)	25 (14%)
Aureomycin (Oral)	25	54	7.0	10 (40%)	22 (88%)
Neomycin (Oral)	25	56	7 2	19 (76%)	22 (88%)
Penicillin (Intraduodenal)	19	56	7 1	11 (58%)	12 (63%)

* Duration of hypotension up to point when 40 per cent of shed blood had returned to the circulation from the reservoir

TABLE VI

Experimental Hemorrhagic Shock
Effect of Antibiotics Administered Parenterally

Drug	Number of Dogs	Bleeding Volume (ml /kg)	Hypotension Period* (hrs)	"Taking-Up" Incomplete at 8 Hours	Survivors
None	185	53	4 8	12 (6%)	25 (14%)
Clostridial Antitoxin	20	54	5 8	8 (40%)	2 (10%)
Clostridial Toxoid	20	58	5 9	4 (20%)	6 (30%)
Penicillin (Intramuscular and intravenous)	20	58	6 3	5 (25%)	8 (40%)
Aureomycin (Intravenous)	17	50	5 8	4 (24%)	4 (24%)
Aureomycin (Intraportal)	10	51	6 5	3 (33%)	8 (80%)

* Duration of hypotension up to point when 40 per cent of shed blood had returned to the circulation from the reservoir

tion Dr Shorr and his collaborators have found a toxic substance in liver which they regard as the product of anoxia

Shorr I should like to ask whether we are entitled to use the word "toxic" with respect to ferritin A substance obviously concerned with normal physiology becomes toxic only by virtue of abnormal concentrations Whatever role this material may eventually be shown to have in circulatory homeostasis, we think it is justifiable, at present, to regard it as a physiologic metabolite which, under certain circumstances, appears in excess in the circulation In contrast, a toxin is something foreign, or an endogenous substance which is poisonous and which arises as a result of tissue breakdown

Fine. Isn't it correct, Dr Shorr, to use the word "toxic" whether the substance is exogenous or endogenous, provided it is deleterious to the peripheral circulation?

Shorr Only if you make it clear that you recognize that, as in the case of ferritin, it is a physiologic metabolite, part of the normal economy of the body, not produced by autolysis but by normal metabolic processes, and that its deleterious effects when present in excess are comparable to the deleterious effects of epinephrine and norepinephrine in pheochromocytoma

Haley Dr Fine, that material is not toxic under any other circumstances You can inject enormous doses into a normal animal without producing a toxic reaction I do not think it should be called toxic unless the exact meaning under these conditions is stringently defined

Fine· Dr Shorr has called it a toxin, and he has defined the conditions I will only refer to his statement about ferritin I shall come to that

EFFECTS OF ANTIBIOTICS UPON SHOCK

Since bacteria, especially the gas bacilli, are normal inhabitants of the dog's viscera, particularly of the liver, we used parenteral penicillin in large doses, but without substantial benefit From other studies we were led to try aureomycin instead (4 5,6,7) Certain data suggested to us that intestinal bacteria might be incriminated, either as invaders of the liver during shock via the portal vein, or as elaborators of an absorbable toxin within the wall or lumen of the gut Since aureomycin intravenously in the dog is not as effective as oral administration and since the control of the intestinal flora by this drug requires several days of therapy, we pretreated the dog for six days with oral aureomycin and added a large priming dose several hours before the experiment The results demon-

this question is probably no, although this is still somewhat in doubt

In Table VI the data are given for 20 animals treated with clostridial antitoxin Bleeding volume was the same There was a slight prolongation of the pretransfusion period, but the survival rate was only 10 per cent

Shorr When was the antitoxin given?

Fine. Continuously throughout the experiment and as priming doses before the experiment

A clostridial toxoid,* which was developed by Logan at the University of Cincinnati and tested by Altmeier, has been found to produce full immunity against the Clostridia when given according to a certain technique In a series of 20 animals we found very little protection provided by the use of this substance

The results with penicillin given parenterally, both intramuscularly and intravenously, throughout the experiment and for a number of days preceding the experiment, were also equivocal, that is, only a 40 per cent survival rate

Aureomycin, given intravenously, also yielded a poor result But when the aureomycin was put into the portal vein and given by continuous drip throughout the experiment, 80 per cent recovery was obtained

Burch Do you think aureomycin per se has any metabolic influence on the liver?

Fine I do not think so, and I shall soon give my reasons

Selkurt May I ask a question on the technique for the portal infusion and the precautions necessary, surgically speaking?

Fine We put a catheter into the splenic vein by one of two ways We do it, immediately before starting the experiment, by making an incision, bringing the spleen and its pedicle into the wound, cannulating the vein, and closing the incision after the catheter has been put in Or we prepare the splenic pedicle in advance, plant the pedicle under the skin, let the animal fully recover, and cannulate the vein just before beginning the experiment

Neomycin, which does not eliminate Clostridia from the intestinal flora, and in fact provides a means of obtaining an almost pure culture of this species in the dog's feces, is as effective as aureomycin The fact that very little, if any, of this drug is absorbed – I think the figure is under three per cent (8,9) – suggests that it

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* We are indebted to the Lederle Corporation for providing us with this material as well as the polyvalent Cl antitoxin, and to Drs Milan Logan and William Altmeier for instruction in the use of the toxoid

In the control series, 185 dogs were treated according to the method I described, and 86 per cent died Notice that the bleeding volume was 53 ml. per kg, that they remained at the selected hypotensive level for 4 8 hours, and that all but 12 of the 185 dogs took back 40 per cent of the blood in the reservoir in less than 8 hours

In a series of 25 dogs that received aureomycin orally, the bleeding volume was about the same as in the control series, that is, 54 ml per kg They began to take up in an average period of 7 hours in contrast to 4 8 hours, and 10 of them had not taken back the 40 per cent within 8 hours The survival rate in this group was 88 per cent

The results were much the same with neomycin, except that an even larger per cent had not taken back 40 per cent of the shed blood within 8 hours The results with penicillin, given by a duodenal catheter placed several days before, were much better than with penicillin given parenterally The survival rate in 19 animals was 63 per cent Eleven did not take up 40 per cent of the shed blood within 8 hours They had a prolonged period of compensated hypotension The uniformity of the bleeding volume in the various groups of experiments is quite striking

Moore What was the nature of the death in the three animals that died with aureomycin and neomycin? Was it a rather typical terminal episode?

Fine No, they just petered out in much the same way as Dr Remington's animals

Haist· I would be interested in a discussion of the metabolic changes in the liver in shock and the possibility that ferritin or some other humoral substance might be responsible for certain of the metabolic changes Rather than interrupt at present, however, it might better be left for another time

Fine. We can come back to that Some of the data I have will, I think, help to resolve that question.

Which bacteria are involved? Are they perhaps the bacteria introduced into the dog's wounds or blood stream by the experimental procedure? The answer to this question is no, they are not. We have done four experiments in which every precaution against bacterial contamination was taken They were done like a surgical procedure, under the best auspices in a good operating room There was no effect whatever upon the usual course of events Are they the gas bacilli in the viscera? We have been able to culture the gas bacillus from almost every tissue in the dog The answer to

difficult to culture anaerobes from the livers of rats, and that tying off the hepatic artery has a different effect in the rat than in the dog, partly because of the difference in bacterial growth under these circumstances

Shorr Dr Paul Gyorgy has stated that no anaerobes are culturable from the liver of the rat

Fine. Dr Altmeier has some data to the effect that there is a surprisingly high incidence of Clostridia in biopsies from the human liver obtained during operations not involving the biliary tract, at least that is the impression he left upon me when I talked with him * It is interesting that survivors show the same incidence of Clostridia in the liver as do those dead from shock, and that the survivors show a lower incidence of gas bacillus bacteremia and peritoneal invasion than do those dead from shock But the fact that survival occurs even in the presence of a gas bacillus bacteremia is strong evidence in favor of the nonpathogenic or weakly pathogenic state of this organism in these circumstances

Haley Some years ago, Dr Dowdy at Rochester (10) did some work on the gas bacillus He had a number of survivors, and the animals were turned over to surgery for further use He could not demonstrate that the gas bacillus had damaged these dogs to any degree However, immediately upon anesthetizing those dogs, regardless of the anesthetic used, they died Have you done anything with the surviving controls in these experiments that might indicate that there was some myocardial damage, such as Dowdy's dogs showed at autopsy

Fine No, we have not focused our attention on the myocardial damage

Haley I wonder whether it does have any part to play in the shock syndrome as well as in the bleeding tendency

Fine That is a topic which is not my assignment today I feel it is not a crucial factor, but perhaps somebody else is better qualified to discuss it

The widespread destruction of liver tissue by the Clostridia found after hepatic artery ligation, by Chau, *et al* (11), does not occur in dogs dying of hemorrhagic shock Our data, of course, do not exclude the possibility that the Clostridia may be functioning synergistically with other intestinal flora

Table VIII provides data on aerobic intestinal bacteria found in the tissues in shock If the offending bacteria are those present in the viscera, they may be either those invading the portal vein from

* Altmeier, W B, Personal communication

does not influence the Clostridia in viscera And, parenthetically, in answer to Dr Haist, I would add that, presumably, it also does not influence the intermediary metabolism of the liver

BACTERIAL CULTURES FROM ANIMALS IN SHOCK

Additional evidence that the Clostridia are not a crucial factor in the situation is given in Table VII Positive cultures for Clostridia in control animals were obtained in liver, peritoneum, portal vein, vena cava, and bile The incidence of this organism in the various tissues of animals that have survived, whether they have been given an antibiotic or not, is increased The peritoneum is contaminated, there is a bacteremia, and sometimes one gets a positive culture from the bile In animals which die, the results are substantially the same, but there is greater incidence of contamination in the peritoneum, portal vein, and vena cava

TABLE VII

Cultures Positive for Clostridia

	Number of Dogs	Liver	Peritoneum	Portal Vein	Vena Cava	Bile
No Shock – Controls	–	45% (120)	0 (20)	0 (20)	0 (20)	5% (150)
Shock – Survivors (with or without antibiotic)	112	98%	31%	22%	16%	3%
Shock – Nonsurvivors (with or without antibiotic)	108	97%	50%	51%	39%	7%

Figures in parentheses represent number of dogs from which the cultures were obtained

Shorr What about the bacterial counts, are these just "positive" cultures?

Fine These are positive cultures I cannot give the figures on counts

Haist. There seems to be a species difference as far as the ability to culture anaerobes from various tissues is concerned. We tried to culture them from the anoxic limbs of rats in which the circulation had been cut off by clamping for periods of from five hours to fourteen hours, but we were unsuccessful I gather too that it is

that the antibiotic must be acting upon the intestinal flora from the beginning of the experiment The natural inference that all this leads to is that one should take out the intestine and see what happens, and we did However, we have done only a few experiments, and therefore I do not want you to take the data seriously yet In these preliminary experiments, which are only two weeks old, the intestine is removed just prior to inducing hemorrhagic shock These dogs do not become irreversible before eight hours, and they respond to transfusion much like those protected by an oral antibiotic

Let me remind you that the animal is subjected to a continuously fixed level of hypotension and that the blood removed is not returned until the compensatory response of the peripheral vascular system fails In control animals the time required for this to occur is 4 8 hours I am sorry to labor the point, but it is important In the animal given an effective antibiotic, failure of compensation does not develop for some seven or eight hours, and many animals will go for much longer You will notice that 29 out of 50 given aureomycin were transfused after eight hours, when there was still no evidence of failure If bacterial action does indeed account for the development of the refractory state of the peripheral vascular system in hemorrhagic shock, it is surprising that such a process can develop in so short a time as 4 8 hours in control animals This is an average figure It is much longer in some animals and much shorter in others, shorter especially if barbiturates or other anesthetics are used This variability is to be expected, since it may be a function of the rate of accumulation of bacterial toxins and the organism's capacity to detoxify them One will notice that the extent of blood loss is a surprisingly constant figure in all animals and therefore cannot be considered an important factor in this variability

Shorr Is the gut in the untreated animal a site of considerable hemorrhage? How does it look in comparison to that of the animal treated with aureomycin?

Fine The control animal, if not given back more blood than it was deprived of, may or may not show a small amount of blood in the intestine The gut frequently does show a small amount Sometimes it does not show anything really significant Of course, if the dog is transfused in greater volume than it has lost, it will show a considerable hemorrhage from the gut

Shorr Have you examined sections of gut under the microscope? Has the mucosa broken down in your control animals?

TABLE VIII

Cultures Positive for Aerobic Intestinal Bacteria

	Number of Dogs	Liver	Peritoneum	Portal Vein	Vena Cava	Bile
No Shock — Controls	—	2% (110)	0 (20)	0 (20)	0 (20)	2% (150)
Shock — Survivors (with or without antibiotic)	102	23%	9%	6%	2%	1%
Shock — Nonsurvivors (with or without antibiotic)	110	57%	21%	36%	24%	2%

Figures in parentheses represent number of dogs from which the cultures were obtained

the intestine during shock or intraintestinal bacteria which produce an absorbable toxin in the gut wall or lumen during shock This question cannot be answered yet. The data are equivocal. I have pointed out that penicillin given intramuscularly for several days before, and intravenously during, shock, yields a 40 per cent survival rate, but if given by an intraduodenal catheter for several days before and during the experiment, the survival rate is 63 per cent The results with intravenous aureomycin through a systemic vein during shock are poor, if given just before inducing shock, the results are somewhat better, but if given through the portal vein during shock, the results are good

A rather striking bit of evidence suggesting a major role of intestinal flora is the observation that oral pretreatment, either with aureomycin or neomycin, without an oral priming dose, is not effective, whereas a single priming dose of neomycin, which is not absorbable from the gut, yields a 70 per cent survival rate, in contrast to a 45 per cent survival with a single priming dose of aureomycin

Zweifach. When was the antibiotic given relative to the bleeding procedure?

Fine: It is given by gavage into the stomach three hours before the experiment begins

This difference between neomycin and aureomycin is in accord with the fact that neomycin eliminates at least the coliform organisms from the gut much more rapidly than does aureomycin It appears

rest of the animal, exclusive of the gut?

Fine We know about fat deposition in the liver as a result of the use of aureomycin

Haist Might that be related to changes in, or altered absorption of, certain lipotropic factors?

Fine I don't know We see that with intravenous aureomycin more often than with oral aureomycin In man, for example, it has recently been demonstrated that if oral aureomycin is given alone, there is not this lipfanogen effect, which refers to fat deposition in the liver from the use of aureomycin It is most commonly observed in patients who have had both intravenous and oral aureomycin for a long period of time I believe it is not involved in this situation, because neomycin, at least so far as we know now, does not have such an effect on the liver, although studies with respect to this problem have yet to be made

Haist Did you say that neomycin was not absorbed?

Fine Neomycin is not absorbed Only 0 01 per cent of the administered dose cannot be accounted for in the feces

INFUSION OF BACTERIA

Nelson It might be pertinent to tell about our experiments involving the infusion of gram-negative organisms into dogs to see what the effect of these organisms alone may be (12) However, before I do, I think it is important to reflect a minute Dr Fine has stressed freeing these shock experiments of variables, he and so many of us for years have been doing shock experiments without paying strict attention to sterile technique When I was working with Dr Clarence Dennis in the development of a pump oxygenator system, we assumed that for at least three or four hours, bacteria, no matter in what quantities or what variety, would not influence our results, and I think many of the other people who have been doing acute animal experiments have also assumed that bacterial effect would be negligible in a short period of time It was for this reason that we thought it would be interesting to see what the effect of gram-negative organisms alone would be We knew about gram-positive organisms They have been studied for a long period of time, mostly in relation to producing bacterial endocarditis Massive doses can be given, and rapid death or acute metabolic derangements are not seen

We chose the gram-negative organism Paracolobactrum intermedium because it was a contaminant in some of our heart-lung perfusion experiments This organism is a normal inhabitant of the gastrointestinal tracts of dogs and man We gave a pure culture

Fine We are studying the pathology of the intestine now I cannot give you good data yet We have correlative data which are not yet prepared The survivors treated with antibiotics do not show any significant intestinal bleeding There will occasionally be a small amount, but in general the intestines are pretty dry

Selkurt What about the problem of congestion in these intestines, aside from gross bleeding? Is it related at all, and how much of it do you observe in your controls?

Fine If they are not given more than the amount of blood which was bled out, congestion is not an obvious feature of the external appearance of the gut

Haist What is the evidence that the effect of which you speak was due to the absence of a bacterial influence rather than to a reduction of fluid loss or improvement in circulating blood volume when the gut was removed? It is possible that in this instance you are removing a site where fluid may be lost or kept out of effective circulation

Fine The weight of the intestine in the dog dead from shock, which has not been given more blood than was taken away from him, is not substantially greater Whatever change in weight occurs would not increase the percentage of volume loss to such a degree as to complicate the interpretation of the blood volume effect, provided one has not, during the experiment, done such things as administer saline solution or extra blood, and provided the experiment has been done as we have done it

Haist Might aureomycin have an effect by itself, apart from its effect on bacteria?

Fine I suppose you are referring to data in the literature to the effect that aureomycin has some sort of metabolic influence on growth While it is conceivable that aureomycin might affect the intestinal bacteria so as to influence the production of vitamins or deprive the body of certain vitamins, it seems to me that that is not a factor that needs to be considered in an experiment of only a few hours' duration.

Haist I gather from the results of the injections into the portal vein that somehow aureomycin would have a direct effect on the liver Is that correct?

Fine I would have thought so three months ago Now I wonder whether it is an effect on the liver or whether it is simply forestalling trouble for the liver by taking out organisms that are otherwise getting through from the intestine

Haist Does aureomycin produce metabolic changes within the

rest of the animal, exclusive of the gut?

Fine We know about fat deposition in the liver as a result of the use of aureomycin.

Haist Might that be related to changes in, or altered absorption of, certain lipotropic factors?

Fine I don't know We see that with intravenous aureomycin more often than with oral aureomycin In man, for example, it has recently been demonstrated that if oral aureomycin is given alone, there is not this lipfanogen effect, which refers to fat deposition in the liver from the use of aureomycin It is most commonly observed in patients who have had both intravenous and oral aureomycin for a long period of time I believe it is not involved in this situation, because neomycin, at least so far as we know now, does not have such an effect on the liver, although studies with respect to this problem have yet to be made

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We chose the gram-negative organism Paracolobactrum intermedium because it was a contaminant in some of our heart-lung perfusion experiments This organism is a normal inhabitant of the gastrointestinal tracts of dogs and man We gave a pure culture

which had fourteen hours' incubation Much to our surprise, we found that the simple infusion of organisms from the culture caused rapid death in the animals, often as early as two and a half to three hours, and going on to thirty hours, but within the time of an average acute experiment The metabolic derangements seen were characteristically those of metabolic acidosis: a depression in the arterial pH, a fall in the whole blood carbon dioxide content, and a rise in organic acids as measured by a rise in lactic and pyruvic acid, all of which had been described as occurring prima facie from hemorrhagic shock alone In addition, these organisms are hemolytic and are capable of producing a rise in plasma hemoglobin

I mention these things just to indicate what infusion of so-called nonpathogenic gram-negative organisms into dogs will do Perhaps this may be a clue to the vitiating factor that exists in shock In other words, as a person or a dog is subjected to long periods of hypotension, are the normal protective barriers, which keep the potentially toxic organisms from the systemic circulation, jeopardized? Perhaps, there is an autoinoculation from the animal's own gastrointestinal tract

Fine By the use of radioactivity-labeled colon bacilli, we have been able, in certain circumstances, to demonstrate the entrance of organisms from an apparently intact gastrointestinal tract

Nelson I think the two conclusions that one can draw from the role of gram-negative bacteria are these first of all, that an infusion of gram-negative bacteria, particularly the paracolon bacillus, is able to cause rapid death, preceded by metabolic acidosis and coagulation abnormalities in some instances In other instances, there are gastrointestinal hemorrhages This is all possible by bacterial action alone

Moore How about hypotension?

Nelson We did not quantitate that Obviously the dog was in shock We did not have continuous tracings of blood pressure because we did not want to infuse any other bacteria With the means at hand, I was not able to satisfy myself that we would not be introducing other bacteria if we did that

I think the second conclusion to be drawn is that acute animal experiments, especially those which involve the perfusion of blood, must be done under sterile technique, because if we inadvertently infuse an unknown number of gram-negative organisms, we are introducing occult variables which will render our data invalid

Osserman What was the approximate quantity of bacteria in-

jected into these animals, and were the bacteria suspended in a plasma medium?

Nelson. A fourteen hour culture of organisms which had been grown in broth was administered The broth was discarded after centrifugation, and only the residue in the bottom of the tube was administered to the dog This was readministered in about 50 ml of saline

Osserman Did you try injecting killed bacteria?

Nelson We have not done that as yet

Moore Did you recover the bacteria from the animal's blood stream?

Nelson· It was interesting to follow the course of the bacteria in the blood stream Immediately after infusion, the blood stream was absolutely loaded with bacteria

Moore Which would grow?

Nelson That is right, they grew out on the blood culture plate At three to five hours, however, the dog was able to clear the blood stream of the organisms, so that at five hours after infusion, in those animals which were yet alive, we got a smaller number of colony counts, but the organisms were still there, and growing

PRODUCTION OF SHOCK BY LIGATION OF A LOBE OF THE LIVER

Howard Dr DeBakey and I have been studying somewhat the same problem as Dr Fine, but we have been approaching it from the angle of primary hepatic injury rather than primary circulatory damage

If we ligate one lobe of the dog's liver, the dog routinely dies six, eight, or twelve hours later in shock (Figure 11) By one lobe, I mean one of the six or seven divisions that the dog has

Lobe Ligated	Number of Dogs	Died Within 48 Hours	
		Number	Percentage
Large left lobe	5	4	80
Small right lobe	5	5	100
Total	10	9	90

FIGURE 11 Hepatic injury Effect of ligation of hepatic lobe upon control series

If we give this dog oral aureomycin ahead of time and continue it after the injury is performed, the dog still dies (Figure 12)

which had fourteen hours' incubation. Much to our surprise, we found that the simple infusion of organisms from the culture caused rapid death in the animals, often as early as two and a half to three hours, and going on to thirty hours, but within the time of an average acute experiment. The metabolic derangements seen were characteristically those of metabolic acidosis: a depression in the arterial pH, a fall in the whole blood carbon dioxide content, and a rise in organic acids as measured by a rise in lactic and pyruvic acid, all of which had been described as occurring prima facie from hemorrhagic shock alone In addition, these organisms are hemolytic and are capable of producing a rise in plasma hemoglobin

I mention these things just to indicate what infusion of so-called nonpathogenic gram-negative organisms into dogs will do Perhaps this may be a clue to the vitiating factor that exists in shock In other words, as a person or a dog is subjected to long periods of hypotension, are the normal protective barriers, which keep the potentially toxic organisms from the systemic circulation, jeopardized? Perhaps, there is an autoinoculation from the animal's own gastrointestinal tract

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Moore· How about hypotension?

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I think the second conclusion to be drawn is that acute animal experiments, especially those which involve the perfusion of blood, must be done under sterile technique, because if we inadvertently infuse an unknown number of gram-negative organisms, we are introducing occult variables which will render our data invalid

Osserman What was the approximate quantity of bacteria in-

Fine In what dose?

Howard· Five hundred to 1000 mg a day.

Shorr May I ask how you ligated the lobe?

Howard These experiments were done by mass ligature, including the complete blood supply of the lobe Without any question, that lobe was completely ischemic at the end of the procedure

Fine You had a peritonitis, didn't you, at death?

Howard The degree of infection, the degree of hemorrhage, and the degree of blood-tinged fluid that poured out into the peritoneal cavity were not nearly so marked as in the animals who were not treated

Fine. But the untreated had peritonitis?

Howard. Seemingly

Stead Did you have a group treated by intravenous penicillin?

Howard These are the over-all results of therapy (Figure 14) The antibiotics, unless otherwise mentioned, were given parenterally. By that I mean by intramuscular injection

Therapy	Number of Dogs	Died Within 48 Hours	
		Number	Percentage
Control	10	9	90
Penicillin	14	13	93
Streptomycin	9	9	100
Aureomycin—Orally	16	14	88
Aureomycin i v	26	11	42

FIGURE 14 Hepatic injury Results of therapy

Haist These results are somewhat similar to those obtained by Markowitz and Rappaport when antibiotics were used in dogs with ligated hepatic arteries

ROLE OF INFECTION IN SHOCK IN MAN

Fine From here on I may be going a little far afield and without sufficient data to back up what I say, but I should like to make some reference to man

I would tentatively venture to guess from my data that a patient in shock from hemorrhage who responds favorably to transfusion as late as fourteen hours after injury, as many soldiers in World

Time of Administration	Number of Dogs	Died Within 48 Hours	
		Number	Percentage
Preoperatively and Postoperatively	10	9	90
Postoperatively	6	5	82
Total	16	14	88

FIGURE 12 Hepatic injury Results of oral aureomycin therapy 500-1000 mg daily

Fine What dose did you give?
Howard Five hundred to 1000 mg a day
Fine The doses we give are much larger
Howard If we give the aureomycin intravenously and limit it to the postoperative period, we markedly reduce our mortality (Figure 13) This, I think, bears directly on Dr Fine's work, and my interpretation would be that the organisms do not spring directly from the bowel, for we have not directly injured the bowel We have produced a circulatory collapse, maybe simulating the picture that Dr Fine is presenting But our primary damage is to the liver, where we know the organism exists We have not, under these conditions, improved our mortality by giving oral aureomycin ahead of time

Time of Administration	Number of Dogs	Died Within 48 Hours	
		Number	Percentage
Postoperatively	26	11	42

FIGURE 13 Hepatic injury results of intravenous aureomycin therapy 500 mg daily

Fine Did you give a priming dose, too? What was the interval between the last dose of aureomycin orally and the ligation of the lobe?
Howard Dosing was started a week ahead of time and carried through the ligation and thereafter
Fine It was given on the very day of the ligation, too?
Howard Yes

Howard: I well remember one day when the glucose solution in the hospital became contaminated with a pure culture. I believe it was streptococcus. There were a dozen or more people at one time who were given a pure infusion They had fever, chills, tachycardia, and hypotension

Sharpey-Schafer. We obtained some data on these severe infections in man There were two groups with low blood pressures. When they were catheterized most of them had low cardiac outputs and, we thought, low filling pressures If rapid transfusion was given, cardiac output increased and the blood pressure rose. The increase in output and blood pressure was usually transitory There was another group which appeared to have some real damage to the heart because, no matter how high the venous pressure was raised, nothing happened The blood pressure remained low. I imagine some people will call that irreversible It is not quite irreversible, because some of them, with antibiotic treatment, may recover.

We were also fortunate in working with a surgeon engaged in extensive abdominal resections These operations might take seven hours We found that in order to maintain the filling pressure in the heart, we might have to use about 6 liters of blood We maintained the filling pressure and, we thought, the cardiac output However, the blood pressure eventually fell off completely and more transfusion would not raise it

Fine I wonder, Dr Sharpey-Schafer, whether the patient you referred to in your presentation who was still at a low level of blood pressure after twenty-three days, who presumably had been given drugs, perhaps had not eaten well, had been intubated, and was perhaps in and out of shock frequently during those days, might not be like an animal in hemorrhagic shock for a prolonged period of time in that bacteria might have gotten in from somewhere within the patient's own viscera

I should like to cite a case which demonstrates a situation in which shock may have been due to blood loss or to sepsis, and in which restoring the blood volume did not in the least improve the shock state, while antibiotic therapy did The situation was this A man had a resection of 7 feet of gut for mesenteric thrombosis He was put on aureomycin, and postoperatively began to hiccough On the fourth day he ruptured his wound The peritoneal cavity was then inspected The site of anastomosis was intact There was no peritonitis, but there was a good deal of congestion in the rest of his gut It did not look infarcted The aureomycin was continued

War II did, that such a patient is still free of a telling amount of circulating bacterial toxin. I do not wish to suggest that the toxin in many necessarily derives from intestinal flora in the gut or from those normally present in the viscera; they are more likely to be derived from bacteria introduced into the wound, whether the wound is a massive trauma, a gunshot wound, or a burn. Frequently, however, it is important to remember, from clinical experience, that the worst wounds and the most devastating ones are those in which there are intestinal flora which are universally present on the skin of the lower part of the body. Refractoriness to transfusion may depend on the degree of bacterial contamination, balanced by the degree of the patient's immunity to the particular species of contaminating organisms, and the effectiveness of antibiotics, whether applied prophylactically or therapeutically.

Dr Churchill has always emphasized the difference between hemorrhagic shock and wound shock, as seen during the war. There is a clue here, I think, as to what that difference might be In spite of the fact that the blood loss was fully replaced, many of these men were in shock and died Why wasn't sepsis an obvious inference as the explanation for the persisting shock? Presumably because those wounds did not look infected

I think it is important, in such a situation, to remember that the individual in shock cannot mobilize his defenses and demonstrate, by constitutional or even local signs, that there is sepsis in such a wound The burden of proof rests with those who say there is no sepsis in that wound because of the absence of obvious signs of the presence of bacteria It is proper to assume that any open wound is necessarily contaminated Consequently, the only way to demonstrate the absence of such bacteria, theoretically at least, would be to take that entire wound, homogenize it, and culture the homogenate Unless that evidence is available, I would say that wound shock is no more than shock due to blood volume loss plus bacterial action

Moore How about the blood cultures? Would you accept them as bearing on the point?

Fine I would say that was partial evidence of importance, but not sufficient or crucial One can have a fatal septic process without a positive blood culture

Stead We get some data on this from people, particularly the elderly group, who have a little urinary infection They run a high fever, and we find complete circulatory failure We find on top of this a positive blood culture

response whatever at any time.

Sharpey-Schafer You gave fast transfusions without any rise in blood pressure?

Fine: I would say they were not fast, for a liter of blood might take three or four hours

Stead. Had you looked into the possibility of pyrogens entering the blood from the sick gut? If chemotherapy suppresses the growth of bacteria in the intestinal tract, it might reduce the amount of this type of material

Fine I would not know

Shorr I think we have, without doubt, listened to one of the most important advances in the consideration of the shock problem in many a year, and every one of us is going to have to include in his thinking about the shock syndrome a very important determinant derived either from gut breakdown or from products of bacterial metabolism in the gut One begins to think of many other phenomena that are associated with prolonged hypotension and their probable relationship to this well-documented demonstration of the importance of the gut and its products Let us consider, for example, the Dibenamine experiments of Dr Remington, and those that we have carried out The profound degree of hypotension is equivalent to that which has been produced by Dr Fine in his dogs. Why is the animal now free from the undesirable effects which one would expect in accord with the demonstration of the importance of the gut, of the growth of these organisms, and the development of their products? Should we think of a combination of factors operating? How can the experiments with Dibenamine in which hypotensions of 30 mm Hg for long periods of time are associated with recovery of the animal be explained? Would you want to discuss that, Dr Fine?

Fine Our experience with Dibenamine is too limited for me to have an opinion We did try Dibenamine in the late stages of shock to see if we could get rid of the vasoconstriction in the liver

Shorr I think we have to accept the experiments of Wiggers (13), for example, as indicating that the phenomena can be demonstrated

I should like to ask you to consider the matter of the exclusion of the liver in terms of the appropriateness of such an experiment to study the evolution of the shock syndrome It is my understanding that in the course of the hypotension of shock, whether traumatic or hemorrhagic, the blood flow to the extremities is so minimal and the vasoconstriction is so intense that pooling in the extremities can be excluded Hence, the sequestration of blood must take place

thereafter, but he began discharging blood by rectum. Blood was given, estimated to be sufficient by the hemoglobin response, so that there was no significant deficiency in blood volume. The loss of blood was considered to be due to progressive mesenteric thrombosis, but, because of the possibility that the aureomycin might be responsible, it was discontinued. Thirty-six hours thereafter he was in deep shock: cold, moist, pale skin, cyanosis, blood pressure varying from 50 to zero systolic, and anuria. He was then given several transfusions, plus norepinephrine in saline solution. There was no response in any respect whatsoever. After twenty-four hours of deep shock, he was given intravenous terramycin in large doses. No fluid was given by any route except the few hundred ml required to administer the terramycin. Twelve hours after starting the terramycin, he recovered from shock, and he remained out of shock for another five days, during which he received no blood, but did receive saline containing norepinephrine almost continuously. It was evident that he had peritonitis. He died of the peritonitis the day following drainage of the wound. At postmortem he showed complete obstruction of the mesenteric vein. The anastomosis was intact. The terminal ileum showed intense hemorrhagic extravasation in the mucosa and submucosa, but was not gangrenous. This loop was the probable source of the peritonitis.

I consider this a clinical example of shock in which the question of whether the shock was due to blood loss or sepsis was answered by the response to therapy.

Fremont-Smith: Did he have fever during the shock phase when he was cold?

Fine: No, his temperature was about 98° F. most of the time. It rose to 99° or so, but he had a high leukocytosis.

Moore: I think the interpretation of a patient like that is interesting and puzzling. The mesenteric venous thrombosis is a famous way, of course, of producing massive fluid loss into the gut with a tendency toward hemoconcentration. You carried him along with blood, as you mentioned, and his hemoglobin stayed normal, but he could have had quite a low blood volume despite that. I imagine you were still transfusing him when you gave him the terramycin.

Fine: No, we deliberately avoided giving him blood during the administration of terramycin.

Moore: But he had had a lot of blood during the previous couple of days.

Fine: During the first twenty-four hours in shock following the stopping of aureomycin, he got two or three transfusions, with no

now appears to be very important, but this factor may be simply an additional component of the total stress which finally produces the picture of shock. Bleeding an animal 45 ml. per kg, plus bacterial invasion and bacterial toxins, will produce shock. Further study may prove that if we control the bacterial factor, the animal will require a bleeding of 55 to 65 ml per kg. to produce the same picture, but the shock syndrome itself may not be very different.

Perhaps the most important point here is the question of whether the hemodynamics in shock involving bacterial invasion are really the same as the hemodynamics of shock which do not involve this factor. It is possible that there are important differences. The prior discussion pointed up the fact that one of the things that may be happening in shock, to the detriment of the animal, is an improper redistribution of blood due to an overactivity of the sympathetic nervous system, suggesting that if we prevent the body from overcompensating, we may prevent the development of irreversibility.

We would not expect the action of bacterial toxins to be localized to specific organs. If they are acting by damaging endothelium, producing vasodilatation, and the like, we might expect a priori that they would have a more generalized effect than does the sympathetic nervous system. Do we have any information from Dr. Fine's studies, or others, as to whether shock involving bacterial toxins is in effect hemodynamically the same as shock from pure hemorrhage, or is that simply one of the questions that must await further studies?

Fremont-Smith: I have a few data on typhoid vaccine fever and malaria fever in man, particularly on the former. During the chill stage, during the rising fever stage in which there is a tremendous vasoconstriction in the skin, and the blood flow through the capillary bed comes to a standstill and stays at a standstill until the temperature has reached its peak, there is obviously a very gross redistribution of blood, because in spite of a vasoconstriction which is as intense as can be found anywhere in the skin, the blood pressure is down. In a number of instances, it is close to shock levels, with a systolic pressure between 50 and 60 and a diastolic which is imperceptible. The patients look as if they were in shock.

There seems to be some evidence that the blood redistribution in vaccine fever is different from the redistribution in a faint, for instance, where you have the same intense vasoconstriction in the skin. Apparently, the patient in a faint has a vasodilatation in the muscle, whereas in the fever I think there is some evidence of vasoconstriction in the muscle as well.

within certain viscera. Among these, the major one is the liver.

A number of people have attacked the shock problem by trying to isolate the influence of one factor or another, as for example, removing gut and the liver. If you remove the organs in which the sequestration occurs, can you expect that under those experimental conditions you are observing what takes place in the course of shock? If not, are these experiments appropriate for the purpose for which they were designed?

Fine: We were so concerned about the question of the liver's pooling action in shock that, as a control for further study, we produced an Eck fistula in order to avoid congestion in the portal circulation (14) We did the Eck fistula in two ways, a total Eck fistula and a fistula in continuity. The fistula completely avoided the portal and intestinal congestion, but this did not influence the shock state in the slightest

Shorr. Was the liver congested?

Fine. In radiographs of the circulation, the liver shows generalized vasoconstriction. The congestion is distal to the liver, i.e., toward the intestine, so that a dilated main portal trunk is seen, along with intrahepatic venous constriction (15)

Shorr Would you say there was no pooling in the liver?

Fine: I don't know whether there was pooling because we did not weigh the liver or measure liver volume to see if there was incarceration of blood But we know that we avoided incarceration of blood in the portal vessels below the level of the liver and in the gut, and prevented intestinal hemorrhage By measuring portal venous pressure, we found that we prevented an increase in venous tension in the main portal vein

Nickerson I should like to raise what I think is a fundamental question in regard to the way in which we fit data such as Dr Fine's into the total picture of shock. There is no question but that a wide variety of stresses are capable of producing a shocklike condition in animals Hemorrhage has been one of the most commonly studied Dr Remington has pointed out that acute changes in electrolyte balance may produce a similar picture Dr Fine's data show convincingly that bacterial toxins of one kind or another can produce or contribute to the production of shock

However, I question whether the information we have received this morning fundamentally changes our ideas about the development of shock, the mechanisms by which the body attempts to cope with it, and why the body sometimes overcompensates In most studies in the past, we have neglected the bacterial factor, which

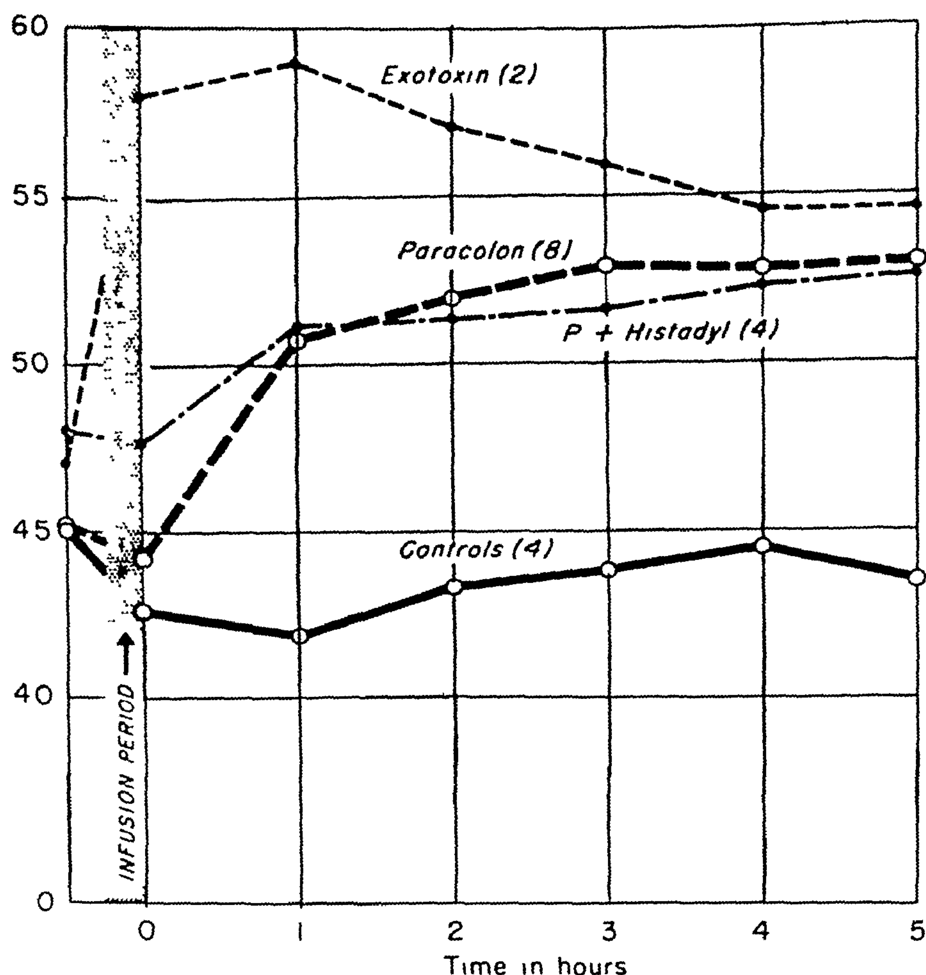


FIGURE 15 Average hematocrit values for dogs receiving paracolon bacteria, paracolon exotoxin and control infusion of saline Reprinted, by permission, from Nelson, R M Metabolic effects of paracolon bacteremia *Ann Surg* **34**, *885 (1951)*

is all the more impressive in the face of red cell destruction by hemolysis It is obvious where this fluid goes Autopsy findings show that there is edema in the gastrointestinal tract, the pulmonary parenchyma is edematous, and there are serosanguineous infusions in the serous cavities I am sure the fundamental mechanisms for circulatory failure can be resolved by this simple phenomenon It harks back to the fact that we need more basic information on the metabolic derangements that are associated with severe infection We know a lot about the physiology of the bacteria We know a lot about the immune response of the host, but we have very little in the way of study of the metabolic derangements of a host in bacterial infection

I don't think one gets a generalized phenomenon with bacterial toxin, at least at the level of the reaction to an intravenously injected bacterium. The sympathetic nervous system is greatly stimulated, and it is possible to show that the vasoconstriction is sympathetically induced, because where there has been sympathetic involvement, as in Raynaud's cases, on one side, vasoconstriction occurs only on that side during the rising temperature phase.

Nickerson: The picture is obviously complex. I believe that enough work has been done on the mechanism of action of pyrogens to indicate that at least a large part of their action is on the hypothalamus and is mediated through the sympathetics Indeed, the response to pyrogens may be altered markedly by the administration of agents of the Dibenamine type However, we also know that bacterial toxins can have a direct local effect Do we know, even in a preliminary way, which of these factors is involved in the potentiation of shock by bacteria? Are there any hemodynamic measurements in animals with and without antibiotic protection?

Fine I can only say that we have not seen any difference in the manifestations of peripheral vascular collapse, no matter how the collapse is caused, whether by sepsis, hemorrhage, tourniquet shock, or whatever you please When I started my discussion, I said that I was dealing only with the peripheral vascular collapse and the clinical manifestations of that condition Dr. Zwiefach has beautifully demonstrated what is going on in the peripheral circulation Anything outside of the peripheral circulation, it seems to me, is another and much more complicated story than I am dealing with I am dealing only with the phenomenon of persisting deficiency of flow in the peripheral vessels I regard this as the crucial phenomenon, because it produces deleterious effects upon tissue function and therefore determines the death of the animal when failure of some tissue function is incompatible with life

Nickerson Perhaps the crucial experiments to shed light on this question of similarity would involve a comparison of the protective action of sympathectomy or Dibenamine blockade in animals subjected, as nearly as possible, to a purely hemorrhagic shock, and in animals subjected to shock from direct bacterial action, as in Dr Nelson's experiments

Nelson Figure 15 illustrates the only measurements that I have pertaining to hemodynamic alterations in gram-negative bacteremia. The control dogs have a normal hematocrit throughout the period of observation Those given an infusion of the paracolon bacillus or its exotoxin (Seitz filtrate) all show a rise in hematocrit, which

TABLE IX

Effect of Applying the Artificial Kidney Upon the Blood Chemistry in Hemorrhagic Shock

Group		No.	Glucose (mgm %)	Urea N (mgm %)	K (mEq /L)	Na (mEq /L)	Cl (mEq /L)	pH	CO_2 (mM /L.)
Control Values		30	156	20 5	3 8	146	112	7.42	18 5
Shock	Before Treatment	30	77	36 6	5.7	145	113	7.22	10 7
	Treatment Kidney Plus Transfusion	10	85	18 8	3 9	146	100	7 45	17 1
	Treatment Transfusion Only	20	76	46 6	5 9	148	112	7 29	13.0

Moore: If you were to draw a line of the collapse of the dog on your chart (Figure 15), where would the slope be steepest? Would it be before the hematocrit gets up, or would it be along about the second or third hour after the hematocrit is up?

Nelson: There is a difference in the groups. First, the exotoxin group—I hesitate to say too much about them, since this group consisted of two dogs — with a single injection, the dog may or may not recover. Second, in the paracolon group, in some dogs, death occurred at two and a half to three hours, and one dog went thirty hours But the slope roughly parallels the hematocrit line.

Fine: The data in Table IX are taken from analyses on animals that died of hemorrhagic shock. If the data that I presented this morning mean that these are animals suffering not only from blood loss but also from bacterial invasion, it may bear on your point, Dr. Nickerson. These animals were treated with the artificial kidney during hemorrhagic shock in order to see what derangements in electrolytes and intermediary metabolism, as far as we could determine them, were significant in the course of events. Blood glucose, urea nitrogen, potassium, sodium, chloride, pH, and CO_2 were determined before and after applying the artificial kidney Normal values were restored as a result of use of this apparatus. The dogs died in irreversible hemorrhagic shock with no observable change from the usual course of events, in spite of restoration of the normal values (16)

Bradley: We measured hemodynamic changes in normal and hypertensive humans during the hypotensive phase following injection of typhoid vaccine or pyrogens (17). We have been unable to find any qualitative difference between the hemodynamic changes observed in that stage and those seen in shock There may be quantitative differences As in traumatic shock, there is a marked drop in cardiac output and there is vasoconstriction in the kidney I am unable to say whether the vasoconstriction in the kidney under these circumstances is as great as in the traumatic shock, but certainly the qualitative change is the same

It should be pointed out that the preliminary state in a patient who goes into shock as a result of fever is quite different from the preliminary state in a normal person who goes into shock as a result of trauma During fever the cardiac output is greatly increased, the peripheral resistance is greatly reduced, and the blood flow to the kidney is quite high in man and in dogs But with shock, the renal blood flow is reduced more than one can account for on the basis of the fall in blood pressure.

show a reaction that possibly was reminiscent of the typhoid-malaria chill phase, with a marked vasoconstrictor response, and so on

Shorr I am glad that Dr Moore brought up the cross-transfusion experiments, because, just as with the eviscerate preparation, there is some doubt as to the interpretation of the results of this experimental approach I believe that the results Dr Fine reported today show how misleading the transfusion experiments may be There seems to be no doubt that a factor of intestinal origin profoundly alters the shock picture, yet in prolonged transfusion experiments with a continuous exchange, for hours, between an animal that was going into irreversible shock and a healthy donor animal, Dr Fine found that the donor animal did not experience any deleterious effects This is something for all of us who might use the method to consider

Nickerson. We should always keep in mind that the final shock picture is a summation of a great many things Bacterial toxins which may be coming from the intestine may be extremely deleterious to an animal which is hanging on the borderline of being able to maintain homeostasis, whereas in an animal with a margin of safety – and we know the normal animal has a tremendous margin of safety – that deleterious effect might not be demonstrable

Shorr That calls to mind also the animals which have developed resistance to drum shock As Dr Zweifach mentioned yesterday, these animals withstand a type of hemorrhagic shock which is lethal in untrained rats They undergo the same degree of hypotension, and presumably have the same gut factor operating, nevertheless, the resistant animals recover Thus, it is clear that there is a summation of effects and a cooperation of a variety of factors

Fremont-Smith Aureomycin is given to the dog, whereas the rat is bounced around, and in both cases the animal is protected against a similar kind of shock I think that is quite interesting

Shorr When Dibenamine is given before the induction of shock, the animal is protected because, with the same degree of hypotension, the peripheral vasodecompensatory changes, which can be so deleterious, are avoided As long as the secondary changes of a metabolic nature are avoided as well, then the deleterious factors are not overwhelming

Burch It seems to me that if one could develop a standard dog such as Dr Fine is describing, it would be possible to titrate the deleterious factor, such as infection

Shorr Yes Dr Zweifach raised the point that sometimes a

Moore. I think it is interesting historically to contemplate the various periods of the shock problem in which circulating toxin factors have been incriminated. One thinks back to Cannon's work, then the long gap when the Blalock school of thought predominated, then Dr Aub's work, and now Dr Fine's work Every time that such an approach involving toxins has come up, cross-circulation experiments have been designed to cast some light upon it, with a possibly rather naive assumption that if there is something circulated in the shocked dog that is actually deleterious, then a cross-circulation experiment should shock the recipient dog

Fine: We have, on our laboratory agenda, the intention of doing a perfusion of the intestine to maintain its integrity during the exposure of the rest of the organism to the same degree of shock as we have usually produced You may recall that we did the cross-circulation experiment on the liver (18) When we gave arterial blood into the portal system, we found a substantial protective effect What the protective effect consisted of, I do not know. One had a choice between the inference (*a*) that the liver normally is in some way engaged in maintaining some kind of homeostatic mechanism in the peripheral vessels, and the inference (*b*), as Dr Shorr's data suggested, that the liver produces an undesirable substance as a result of deficient flow of oxygenated blood We hesitated, from the data we had, to draw either inference In the light of our data, we could only say that what was done for the liver was that it assisted in sustaining its normal function With respect to infection, this would be detoxification, and to this extent cross-circulation might have been a helpful thing. I would forget all about that for the time being, but we plan to do the same kind of experiment on the intestine, where we now think the chief trouble lies, to see if correcting deficiency of flow through the intestine will forestall the development of irreversibility

Moore Also, how about taking the blood from the shocked animal and simply putting it into an unbled animal or into an animal that is bled the same volume so that there is no net volume change? Does it produce shock in the recipient dog?

Fine That has been done many times, but it seems that what the shocked animal is suffering from is a continuing dose of poison, whereas if you simply take a given volume of the shocked dog's blood and put it into a healthy one, you give the latter a fixed amount of undesirable material to deal with, and he probably can handle that much

Moore But I should think in the process of handling it, he would

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standardized animal may not allow for the participation of all the factors which normally operate in circulatory homeostasis If, for example, with a Lamson bottle, you should completely curtail the renal contribution, then, while you have a standardized animal, you also have one which is deprived of a very important participant in circulatory homeostasis.

Nickerson: If I recall correctly, Harold Wiggers (19) used the Lamson bottle in some of his first experiments with Dibenamine, and in the presence of the blocking agent he obtained good protection, which may mean that some circulation through the kidney persisted.

Zweifach: Dr Wiggers and his co-workers used the Lamson reinfusion reservoir technique but followed a graded hemorrhage procedure

Moore· But with Dibenamine the animals began to take up much sooner, didn't they?

Nickerson· Yes

Moore Dr Fine, I asked about the three dogs who died under aureomycin (Figure 11) In them the infectious factor had, presumably at least, been dissected out, and yet they went ahead and died Perhaps this is germane to the point we are discussing now.

Fine I should have pointed out that those three dogs lived decidedly longer than the unprotected animals, but we did not call them survivals because they were dead within twenty-four hours We called it a survival if the animal was frisky and able to eat and run around the next day and continued to do so thereafter.

Stead: You are coming back to what Dr. Remington said yesterday, that essentially we are studying the way animals die. We have postponed that time by the use of blood and antibiotics Now that you know about the gut factor and the role of antibiotics in it, you will eventually make yourself a new irreversible shock preparation. All you have to do is put your blood pressure bottle at 20 or 10 or whatever it takes to damage the animal sufficiently

Fremont-Smith You will have wound shock in aureomycin-treated patients, and exactly the same problem will come up then, too

Shorr: The factors that basically regulate peripheral circulatory homeostasis are also basic to the compensatory and decompensatory peripheral circulatory changes which occur in shock If these mechanisms which we in our laboratory have emphasized were not involved, and the only principle responsible for circulatory deterioration were a toxin, then we should expect that in Dr Fine's

cross-perfusion experiment the donor animal with a healthy liver would have been able to remove the toxin and thus protect the other animal from shock. This was not the case, except when the viviperfusion of the liver was begun at the start of the bleeding. When it was begun only after there had been significant taking up of blood from the reservoir by the shocked animal, the animal continued irreversible and the donor provided no protection (18). Under the latter circumstances the peripheral circulatory decompensation, which is temporally associated with ferritinemia and breakdown of the liver VDM inactivation mechanisms, was well established at the time the viviperfusion of the liver was begun. What I mean to make clear is that we have observed no condition in which circulatory decompensation, of the type that we have described as associated with ferritinemia, fails to occur during irreversible shock, and that whatever the effects of "toxic" materials derived from the gut or liver autolysis, they are superimposed upon a deteriorated peripheral circulation.

Fine: I hope I did not give the impression that administering an antibiotic to an animal kept at a fixed level of hypotension of 30 would allow the animal to live forever. Surely, if you kept him in such a state for a long period of time, he would begin to get the effects of tissue damage, and that tissue damage might hit the heart or the brain or the liver, and he would die from the loss of a vital organ's function

Moore. Yes, but it is the direct definition of that precise tissue-damaging process that we must move on to, as Dr. Zweifach said yesterday The deterioration after hypotension remains the problem, and the mere fact that it is delayed with antibiotics does not in any way lessen its importance, particularly when you look at the human in whom the antibiotics do not prevent shock.

Fine: Surely, if you open up the aorta in a man, he will die, and die fast If you make a small hole in his aorta, he is going to die unless you plug it up The question is whether we are, in these experimental situations, simulating something like the state of affairs that we have to deal with in the clinical problem

Shorr· You are in danger of insisting that death cannot be due to shock in the absence of the bacterial or gut factor.

Fine: I do not want to make that inference However, I do say that when a patient shows the classical features of shock as a result of hemorrhage and does not respond to an adequate replacement of blood volume, one must consider whether or not the failure to respond is due to sepsis If treating sepsis with an effective anti-

standardized animal may not allow for the participation of all the factors which normally operate in circulatory homeostasis. If, for example, with a Lamson bottle, you should completely curtail the renal contribution, then, while you have a standardized animal, you also have one which is deprived of a very important participant in circulatory homeostasis.

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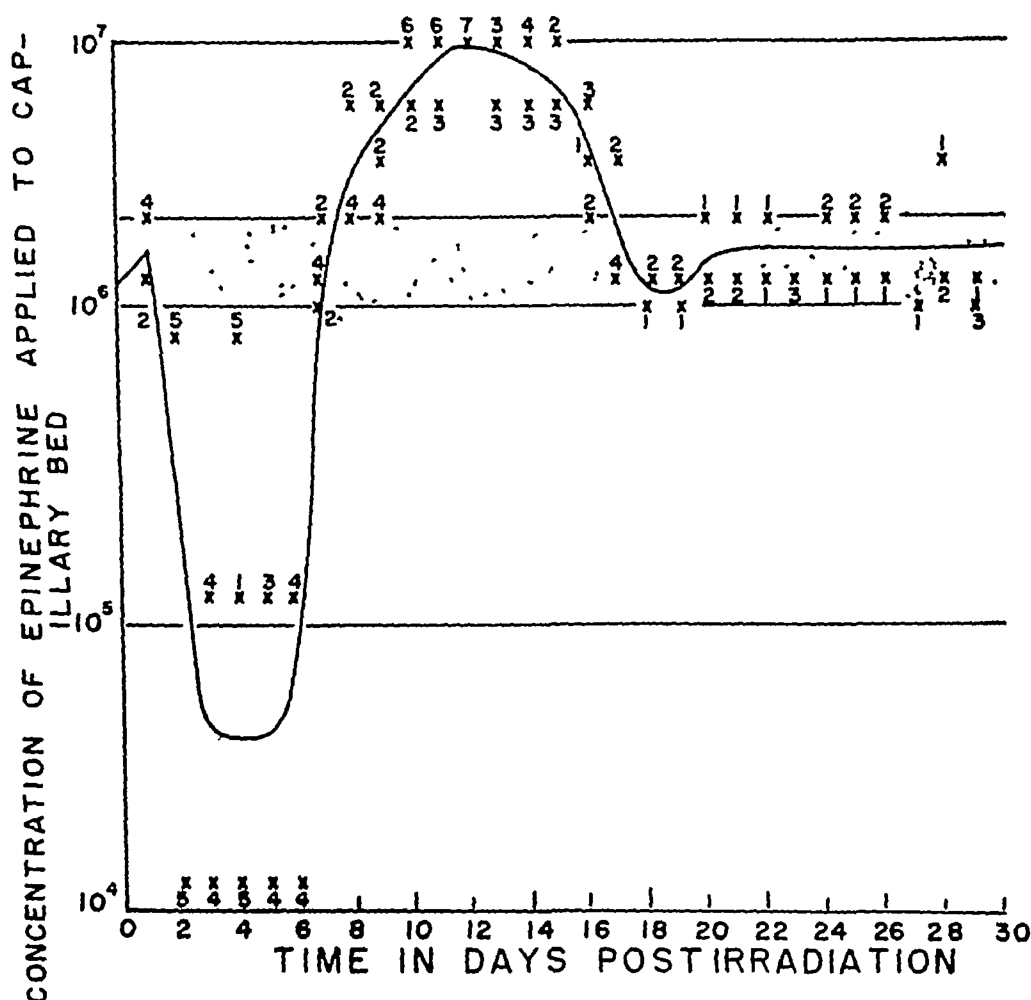


FIGURE 16 Smooth line represents average response of precapillary sphincters and terminal arterioles to topical epinephrine The numbers signify the number of animals responding to a particular concentration of epinephrine The dotted area represents the spread of normal animal response, 81 per cent responded to a concentration of 1.2×10^6 Reprinted, by permission, from Haley, T J, *et al.* Presence and identity of vasotropic substances in blood of rats subjected to acute whole body roentgen ray irradiation *Am J Physiol* **168**, 628 (1952)

day to day, but over the period of the last three years. Whether that would be an LD_{50} dose for some other laboratory, I would not want to say. There are certain features, concerning an LD_{50} of irradiation, which I attempt to avoid One is the fact that the slope of the lethality curve approaches 1, so that a small amount over or under 600 r can produce some profound changes in the rate of mortality and the total over-all mortality Usually I define the dose as 600 r, and attempt to forget the LD_{50} terminology

In Figure 16 we plotted epinephrine sensitivity against time

biotic does not then cure the patient, it may be that it is a sepsis for which we do not have an effective antibiotic, or it may be another factor. I don't presume to interpret what that other factor may be.

IRRADIATION SHOCK

Shorr. It might be appropriate, at this time, to ask Dr Haley to tell us something about irradiation shock, since this condition has also been shown to be affected by antibiotics.

Haley. We again come to a situation of rigidly defining the conditions under which the work was done * In the first place, the amount of X-radiation given, whether given regionally or to the whole body, was 600 r The animals investigated thus far have been rats

In the radiation syndrome one deals with many factors, not the least of which is the destruction of the formed elements of the blood We did not, in any sense of the word, make any blood counts. That had been well documented by Bryan and Suter at Rochester (20), including the early phases in the first fifteen minutes up to the first twenty-four hours, and each day thereafter for a considerable period We did not use any antibiotics Howland at Rochester (21) has been able to demonstrate that, to some degree, aureomycin takes care of the bacteremia which is present The bacteremia, which develops on the third day, is highly specific and not of exogenous origin It is caused by Pseudomonas and Proteus organisms from the large intestine of the animal Thus far we have not found any antibiotics which are entirely effective in controlling it

In so far as the shock phase is concerned, we studied it with the mesoappendix preparation to determine whether the classical picture of shock was present We studied irradiated animals and the blood from irradiated animals Figure 16 illustrates the pattern of response which develops Apparently, in the rat, not much happens until the third day

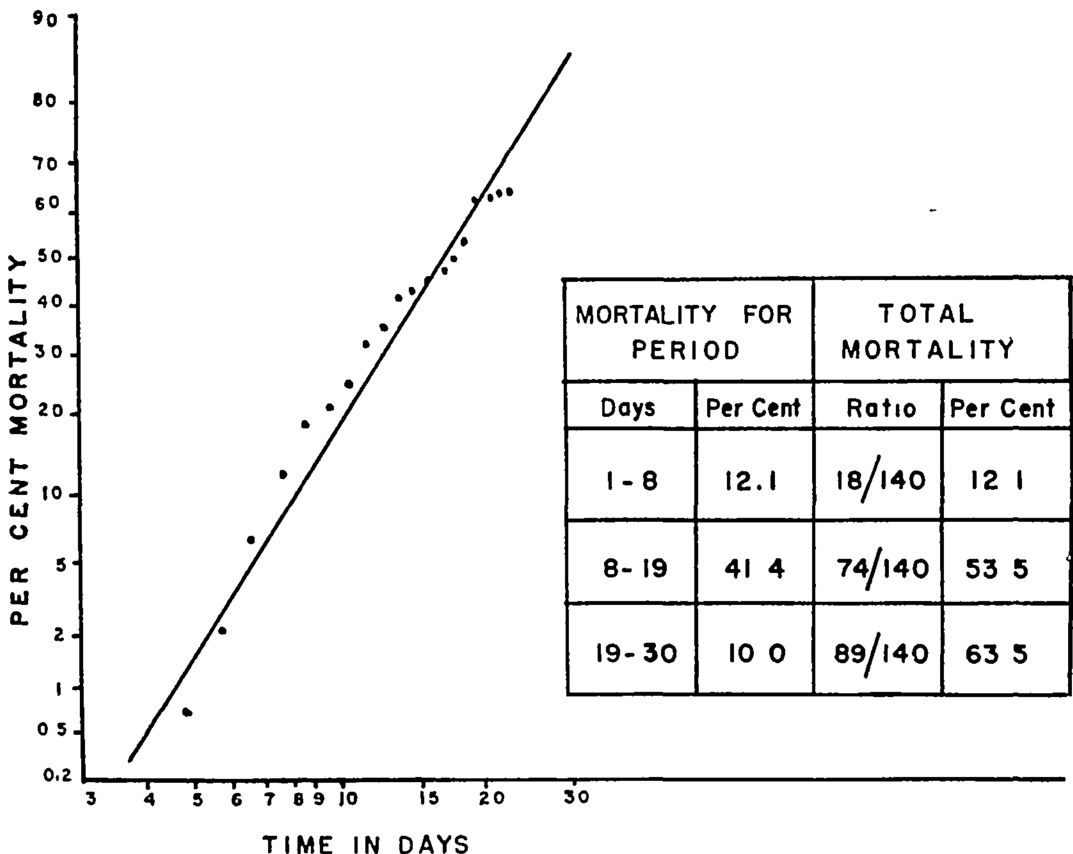
Nelson Is your dose of irradiation an LD_{100}?

Haley It is approximately an LD_{50} If you work with the LD_{100}, things happen too fast, and you cannot, under the circumstances, study much of anything

Nelson How reproducible from strain to strain is that LD_{50}? Do you have to modify your total body radiation dose, or do you find that that is constant from day to day?

Haley For our laboratory it is fairly constant, not only from

* This work was performed under Contract No AT-04-1-GEN-12 between the Atomic Energy Commission and the University of California at Los Angeles



MORTALITY FOR PERIOD		TOTAL MORTALITY	
Days	Per Cent	Ratio	Per Cent
1-8	12.1	18/140	12 1
8-19	41 4	74/140	53 5
19-30	10 0	89/140	63 5

FIGURE 17 Mortality in rats receiving 600 roentgens Reprinted, by permission, from Haley, T J, *et al* Presence and identity of vasotropic substances in blood of rats subjected to acute whole body roentgen ray irradiation. *Am J Physiol.* **168,** *628 (1952)*

Haley Orally, and I believe he did give some parenterally. I do know definitely that a large number were on oral medication

Burton Can you tell us anything about the blood pressure of these animals in this period?

Haley Unfortunately, I did not study blood pressure Dr Lawrence (22) at the University of Rochester did a cross-circulation experiment and found that the recipient animal remained normal after receiving the blood from the irradiated animal. We did some tissue extract experiments in which we took saline extracts of intestine, liver, spleen, and kidney We injected these into rats and recorded arterial blood pressure In all instances we got a hypotension, even during the VEM phase, so that we were not sure as to what the observations meant We even got a hypotension when we blocked a possible histamine action with benadryl, and when we blocked a possible acetylcholine action with atropine

Stead. How do these concentrations of VDM in the blood of

after irradiation. The majority of the normal animals will respond at 1 in 2 million, some few as high as 1 in 6 million The pattern will start off with a slight rise, which we think is not significant, and then by the third day will fall precipitously as far as the response of the bed to topical epinephrine is concerned

In the animals studied after irradiation, there is quite a dispersion. In other words, four animals will respond at 1 in 100,000, and others will respond to epinephrine concentrations as high as 1 in 10,000 The blood of the animals was studied under similar circumstances, and we obtained the same type of reproducible curve. On the third, fourth, and fifth days the responses are down at the lower level of the curve, with the VDM concentration in the blood depressing epinephrine sensitivity and vasomotion The flow in the peripheral vascular bed is extremely sluggish. On the sixth day the animals apparently start to recover. On the seventh day they are back up to the normal sensitivity again Then we have a slight overshoot, which reaches a peak on the twelfth day.

Burton: Is this a titer of the blood of these irradiated animals or is this the sensitivity of that animal's mesentery?

Haley: This is the sensitivity of the animal's mesentery The fact is, we can take blood from irradiated animals, give it to a normal animal, and duplicate this type of curve.

The sensitivity on the VEM side never rises much higher than 1×10^7 epinephrine concentration. It falls off again to normal on about day nineteen, and we get slight fluctuations on out to day thirty. We have not studied animals beyond day thirty

The peculiar significance of this curve and its correlation with death is that in the first week when VDM is present, only 12 per cent of the animals die; whereas during the VEM cycle, 41 per cent die We like to believe that the hemorrhage which can be seen in the small intestine – and there is definitely a slough of the mucosa, both from a histological point of view and from direct observations on the animals – contributes to the death rate during the second week more so than it does during the first week (Figure 17)

All of the toxic factors that Dr Fine was talking about this morning, as far as the bacteremia is concerned, are definitely present in these animals Dr Bennett, one of our group, has worked with antibiotics in attempting to prolong the life of the animals, and the results are not too encouraging But we believe that this is due to the fact that we are dealing with organisms which are not sensitive to streptomycin, penicillin, or aureomycin

Nelson: May I ask how those antibiotics were administered?

one depressor dose being equal to 0.0005 microgram of ferritin, this would give between 100 and 500 doses in that particular sample of plasma.

Burch. What would be the results, then, if Dr. Haley, for example, ran a dilution titration study on one of these materials and used this for comparison?

Zweifach. The radiation experiments of Dr. Haley are most encouraging in that he repeated our work on ferritin independently and obtained precisely the same orders of vasoactivity, using the rat mesoappendix assay.* I would hesitate to advocate carrying the rat assay technique too far as a quantitative tool without a clear-cut understanding of the pitfalls which may be present.

Burch. For a given blood sample, could he run a measurement for quantity to determine what he calls a great deal?

Shorr. I think Dr. Haley has answered that, because with crystalline ferritin he gets about the same vasodepressor effect as we observe.

Stead. This settles the matter I want to know. Your rats have orders of ferritin, of VDM, of the general magnitude of those we were talking about yesterday in shock animals?

Shorr. Dr. Haley, have you attempted minimal bleedings, which ordinarily would not be sufficient to throw an animal into shock, at the time that the ferritin content is high?

Haley. No, we have not tried that.

Shorr. We have observed VDM in the plasma of rats with nutritional cirrhosis (23). Their circulation is maintained under ordinary conditions, but a slight trauma or a small bleeding suffices for these animals to go into shock and die, whereas normal animals would survive the same amount of trauma. It would be interesting to know if the VDM preponderance in your animals predisposes them to shock when the circulation is jeopardized.

Stead. I raise the same objection you raised to cross-circulation, that this is getting rather too simple. These animals have a lot wrong with them besides ferritin. They will die quickly when you bleed them. I think we can all say that.

Haley. Yes, trauma predisposes these animals to death. But there are so many other things involved in this that I am just trying to pick one piece of the puzzle and say these are the data to back up that piece of the puzzle. Perhaps we shall get other data on the bacteremia and the pattern will fit together. It may even be possible that after the liberation of large quantities of VDM in the first

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* Haley, T. J., and Andem, M. R. Personal communication.

these animals compare, in general, with the concentrations in the animals in shock Dr. Zweifach described?

Haley. Ours are extremely high in VDM as compared with his. As far as VEM is concerned, however, our responses there are considerably lower than those found by Dr. Zweifach.

Zweifach There are several characteristics of ferritin activity which have to be taken into consideration Crystalline ferritin, when dissolved in either saline or plasma and injected into a test rat, gives a well-defined vasodepressor assay in concentrations of 0 0005 to 0 001 gamma N When one employs higher concentrations of ferritin, a prozone is reached in which the establishment of vasodepressor activity is no longer possible A variety of side reactions are encountered, which may be related to the effects of ferritin on other systems We are therefore limited, in terms of the crystalline product, as to what we mean by high concentrations Our ability to detect differences in ferritin concentrations between, let us say, 0 001 and 0 01 gamma, the upper limit of our test, varies with the precise concentration of ferritin with which we are dealing This is due to the S-shaped character of the rat test activity curve with different concentrations of ferritin. As indicated earlier, it would be difficult, by testing several samples with concentrations of ferritin ranging from 0 005 to 0 0001 gamma to determine the quantity of ferritin in each of them Samples which are at both extremes of the concentration curve, can be distinguished readily from each other, those in the mid-range, less readily An error of as much as 100 per cent is possible, for example, in an attempt to distinguish between 0 001 and 0 0005 gamma of ferritin

Stead Then we come down to a question of not being able to establish one fact You don't know whether these are large quantities, and Dr Haley says his are large

Zweifach The question at issue here is whether one can arbitrarily compare the activity of an unknown blood sample with that of a known concentration of ferritin I do not believe that this could be readily done without a complicated dilution series and repeated tests to map out the precise shape of the dilution curve with each sample We have not routinely employed such procedures because of the considerable amount of work which would be involved for each sample

Shorr Have you tried to dilute your samples?

Haley Yes, we have been able to dilute them As I have already shown, in equivalence to horse ferritin, it would be a quantity greater than 0.1 microgram, but not 0 5 microgram Based upon

Green: What kind of anoxia were the animals exposed to?

Haley. The animals were exposed to irradiation in an atmosphere of nitrogen with 5 per cent oxygen, for the time it took to deliver a given dose of irradiation They were usually irradiated, if they were rats, in groups of about five. If they were rabbits, they were irradiated one at a time.

Shorr: How long is the period of anoxia?

Haley: It depends upon the total dose of irradiation. At the present time we can give a dose of 600 r in about six minutes.

Shorr: I do not doubt that there could be temporary effects of anoxia, but in this case we do not know what these effects are on specific mechanisms

Haley: Yes, but we do have observations on some rabbits which, after exposure to irradiation and anoxia, had severe circulatory collapse within six hours and went on to exitus. They die quickly, and present the typical picture of shock However, I have not bothered to assay the blood of those animals, because when I was trying to find out whether there was anything circulating after X-radiation, I did not want to impose conditions which might produce the very substance being sought.

Green: Do I understand that six minutes of anoxia was enough to give them some protection against X-radiation?

Haley: Whatever the time limit was required to deliver the total dose

The work under discussion was done a year and a half ago, before we had a double head set-up Now we radiate from above and below with 250 kv machines, so that we get a terrific dosage rate. Prior to that time, work was done with one head, giving a dosage rate one-half the present one

Nickerson· This protective action of short periods of anoxia implies that the effects probably are not the alteration of the VEM-VDM mechanism but involve changes in the metabolic state of certain tissues at the time they are irradiated

Haley: That is a good point

Nelson: I was interested in your answer to Dr. Burton's question, because when you described gastrointestinal bleeding at the third day, that was much different from what we see in humans The Japanese casualties did not show their gastrointestinal bleeding until two weeks later

Haley· Let's define conditions When was it that you saw your first casualties? Six weeks after the irradiation You did not get any of the early ones, so you cannot say that bleeding did not occur

week, antibiotics would reduce the death rate in the second week.

Burton What is it about these animals that makes you feel this has something to do with shock? I have just heard so far that they die

Haley: The simple reason that at the time when epinephrine sensitivity decreases, they are bleeding into their intestinal tract, and the massive hemorrhage continues throughout the second week. We have even seen it up to day nineteen. But it is quite obvious that in such animals, the bleeding may not have begun during the first week. This is consistent with the variations observed in the response to irradiation

One of the points previously raised was the fact that we used serially sacrificed animals and that perhaps the animals taken in the first few days would have been dead on day eight We have also been asked if there is any connection between the appearance of VDM and VEM and the death rate We like to feel, on the basis of observations on some 1500 animals altogether, that after radiation they all go through the VDM and VEM cycles, and that the survivors are better able to take care of themselves However, I have no exact data to prove that particular point

Osserman. Is it possible to increase the mortality in the early period by giving ferritin?

Haley: We have not tried that We have attempted to find out some other things about ferritin in the normal animal It does nothing to the coronary circulation, and it does nothing to the blood pressure response to epinephrine

Osserman: How is it possible to reconcile these results with those of Cronkite and his co-workers (24) who have demonstrated that glutathione and other SH donors exert a protective action against whole body irradiation?

Haley: That happens to be a particular problem which plagued me for a while We worked with some sulfhydryl donors which also inhibited metabolism Unless you give a toxic dose, sulfhydryl compounds have no effect Cronkite (25,26) and Patt (27), as well, have given toxic doses of glutathione but they are actually determining a pharmacologic effect and not a metabolic one

The problem is to reconcile our data not only with this sulfhydryl proposition but also with the anoxic proposition which has been found by Dr Bennett (28) in our own animals We know that if the animals were made anoxic, there would be a tendency to liberate ferritin Yet that is one way of protecting so that they survive, and they survive doses up to and including 1000 r.

a blood pressure determination

Shorr Do you know whether the kidneys, when they form VEM, undergo any type of damage?

Haley. We took kidneys and livers from rats on the third to fifth days The livers paralleled, in ferritin content, the amount of the blood

Shorr. That is, on aerobic incubation the liver slices release ferritin into the medium

Haley Yes, and the kidney during this same time interval was releasing VEM under aerobic conditions During the second week, the liver was releasing VDM

Fremont-Smith. Isn't your titer, then, actually the summation of two contrarily acting substances? You have got both VDM and VEM in there To get the true level of either, you would have to do the antiserum fractionation technique

Haley I believe that would be correct

Most of our work has been designed to attempt to establish what this material was We have had these curves for about a year and a half, and the data on the blood for almost that length of time All the succeeding time has been spent in an attempt to identify positively what the materials were, so that we would have a rational basis for going further

Osserman If the dose of total body irradiation were greatly increased in order to produce a greater mortality rate in the initial period, would you anticipate that the VDM response would still be as striking?

Haley We have not done that, but I would anticipate that if you gave a sufficient dose to be lethal in seven days, the release of VDM would be caused on the first day

Osserman But would there still be a marked predominance of VDM in this initial period?

Haley Yes The predominance of VDM in the initial period is really striking

Green But would it become more predominant with the heavier dosage?

Haley No, but the difficulty is that if you increase the dosage, the animals will never survive to give you the other end of the line

Green How about this first period? Would the VDM be released in any greater concentration?

Haley I would have my doubts that more ferritin would be released

Fremont-Smith You were able to establish that that is ferritin?

early You can say, for those that you did see who had survived up to the point when they were examined, that the bleeding did not take place until that time

Nelson. When does it occur in dogs?

Haley. It varies with the dosage rate It will occur within the first week

Osserman Undoubtedly, there are marked species differences with respect to lymphocyte and leukocyte sensitivity to irradiation Subjected to the same relative dose of whole body irradiation, the rabbit will show maximum white cell depression and bleeding tendency on the fifth or six day in contrast to the rat's much earlier response

Haley· I might elaborate further by pointing out that in the first eight hours the rat loses approximately 50 per cent of his white cells, because he has a 60 per cent lymphocyte count In other words, 60 per cent of his white cells are lymphocytes, and their half-life is about eight hours Thus he has a tremendous loss Furthermore, the level drops down from the initial high and goes along at an extremely low level until approximately the twenty-fifth day when recovery is apparent, but the lymphocyte count is still below the normal level

Burton Have you measured the white cell destruction in the anoxic ones?

Haley I have not Bennett has some data on that, but I have not had the opportunity of going over it very carefully Apparently, you get some of those hematological changes even in the anoxic animals

Burton No, I meant in the protection that anoxia apparently gives from irradiation, has the white cell picture been studied?

Haley There is some destruction of the white cells, but I don't believe it is as pronounced as the destruction in the nonanoxic animal

Howard Do you know whether there is any correlation in your curves between VDM and prothrombin concentration?

Haley No We have recently begun further study of the various factors involved in the blood coagulation process and the picture is rather complicated

Shorr You spoke a little while ago of saline extracts of tissues obtained at various time intervals throughout the syndrome I should like to ask if the tissues were immediately sliced, extracted. and tested, and what you found with respect to the kidney?

Haley We also got hypotension with the kidney This is with

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Haley: Yes, it fitted the characteristics that Dr Shorr, Dr. Mazur, and Dr Zweifach have published for ferritin: depression of vasomotion and decreased epinephrine sensitivity. If you take the plasma and dialyze it, the material will not dialyze. If you inactivate it by aerobic incubation with normal liver, it can be reactivated by cysteine It can be inactivated *in vivo* with a specific antiserum made from rat ferritin We are sure that it is ferritin (29,30,31,32).

On the VEM side, the material fits most of the criteria, but, as Dr Shorr will admit, there is not enough information on VEM to establish definitely what it is

Green: In a group of 50 animals, would all of them show a similar curve whether or not they survived, the 50 per cent that survived as compared with the 50 per cent that died, for instance?

Haley: I believe so, because of the total number we have worked with We have tried out the whole procedure on about 1500 animals, and we get a spread in the amount of detectable ferritin on the third and fourth days By that I mean, one series had 100 to 500 vasodepressor doses on the third day, whereas another series had only 2 to 40 doses on the third day with an increase from 100 to 200 on the fourth day

We like to speculate on the possible mechanisms involved in the release of ferritin It would appear that it is not a direct effect of irradiation

Green If you took the average of the 50 that survived and the 50 that died, would there be any quantitative difference in their curves?

Haley We have not done anything on that exact type of experiment, but I like to believe that all of them go through it, even the survivors

Nickerson: The difficulty here is that you must sacrifice your animals to get each point on the curve

Haley That is right We are getting ready to do dog experiments With these, we shall be able to do serial samples day by day on a single animal, and some of the animals will survive Then it will be possible to give an exact answer to your question

It is possible that this material is directly released as one lump into the circulation, or it could be the radiation sensitivity of the inactivation mechanism I have no data to support this thesis

THE THERAPEUTIC IMPLICATIONS OF CURRENT CONCEPTS OF SHOCK

FRANCIS D MOORE
Department of Surgery, Harvard Medical School

THE THERAPEUTIC IMPLICATIONS of the concept of shock that we have talked about at this Conference are such that I should like to go immediately back to the hospital and study the possible presence of VDM in human patients I should want to take a human patient who obviously has a large adrenal medullary factor early in shock and in whom blood replacement is adequate, a patient whose condition is poor, and administer Dibenamine, then, at or near the same time, carry out the necessary bacteriologic studies to determine if coliform organisms were present But these are ideas that all of you have had after listening to the wonderful papers of the last two days I can imagine that we are all eager to apply the data and concepts presented to the human being.

Confusion about the problem of shock is easy because of the great variety of experimental situations in which shock can be produced, but perhaps that confusion is wise, perhaps it is healthy, because, after all, the clinical problem of shock is equally varied The background of the patient and the situation in which the patient finds himself is just as varied, if not more so, than the experimental situations which have been discussed This is by way of saying that when confused on the shock problem, let's return to the patient because, after all, the shock problem stems from human disease, and we ought constantly to keep this orientation in mind when considering where the laboratory is taking us Thus, I should like to start by giving, very briefly, a number of case histories which seem to bring up some interesting problems, and then perhaps later on discuss some of those patients again in the light of conceptual background

The knowledge and recognition of shock are recent. In the ancient literature one finds few clinical descriptions of what we now call shock At the time of the American Civil War, the syndrome was recognized It was treated with whiskey, morphine, and occasionally by veratrum viride, which was available at that time and was known

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When she came in, she was described by the intern as being in extreme shock, with a pulse of 120 and blood pressure 76/42, she was pale and clammy, very nervous, air hungry, and unable to concentrate on anything. A diagnosis of ruptured ectopic pregnancy was made after examination, and she was immediately started for the operating room. En route there and while under study in the emergency room, she was given rapidly 200 ml. of blood and 300 ml. of plasma. That was simple plasma, started because it could be fetched up first, of course. She was operated on under ether anesthesia. A great deal of blood was found in the peritoneum, and a ruptured ectopic pregnancy was found at the fimbria of the left tube. At that time her blood pressure was zero, her pulse was unobtainable. Clamps were placed on the bleeding vessels. The operation was stopped, in the words of the surgeon, "to avoid any further stimulus of pain or trauma." Blood was transfused, as it had been on the way up, and in fifteen minutes her blood pressure was 90/40. Her pulse came down and her blood pressure went on up above 100. The operation was completed and she went home perfectly well.

The obvious implication is that the early picture we are dealing with is one readily capable of reversal.

SHOCK FOLLOWING A COMPLICATED OPERATION PLUS HEMORRHAGE

The third story I should like to tell is that of a 54 year old man with an advanced cancer in his prostate and rectum. He was prepared for surgery with an intestinal antiseptic of the sulfonamide group. The operation was extremely difficult. He had a frozen pelvis, so-called, and the rectum, bladder, and prostate had to be removed in one mass. He lost a good deal of blood during this procedure, but transfusion was continued throughout the operation. Toward the end of the operation, his condition deteriorated to the point where his blood pressure was falling away quickly despite rapid transfusion and (by our calculations) overtransfusion. He showed the phenomenon, mentioned in our discussions yesterday, of obviously elevated venous pressure. By that I mean that the veins one could see in his pelvis were distended and the arteries were extremely constricted. He bled massively from the distended veins. This bleeding was very difficult to control. His blood pressure fell away to nothing. His pulse became unobtainable. The operation had been going on for about six hours. Of course, we all wondered if we were dealing with something akin to irreversibility. At that point, a plastic catheter was placed in his brachial artery, and by

to reduce the heart rate. The physicians of the Civil War thought that the tachycardia was in itself harmful, an interesting thing when you think of our discussion earlier of the effects of heart rate on cardiac output

SHOCK FOLLOWING EXTERNAL HEMORRHAGE

It might be of interest to recount one of the famous cases of shock in that time, namely, that of General Jackson, who, after making his famous countermarch around the Union Army at Chancellorsville, went out ahead of his troops to reconnoiter at night and was shot by his own pickets Falling off his horse, he staggered back with a broken arm and a severed brachial artery *Lee's Lieutenants** gives the description in the words of Maguire, the surgeon of that Army corps

"His suffering at this time [about six hours later] was intense. His hands were cold, his skin clammy, his face pale, the lips compressed and bloodless, and pulse rapid, weak, and thready. Not a groan escaped him, not a sign of suffering except the slight corrugation of his brow, the fixed rigid face and the thin lips so tightly compressed that the impression of his teeth could be seen through them."

The case history goes on, but, to make it brief, Jackson went on bleeding He was in profound shock, and at that time it was recognized that his shock could not be dealt with unless the bleeding could be stopped, a very important point which we shall come back to later So, under chloroform anesthesia, his arm was amputated. He lived about three more days, during all that time being in a state of what I am sure we would call chronic hypotension, he was probably hemodiluted, and certainly very pale, from the description He died of what was regarded as pneumonia, though it probably was pulmonary infection

SHOCK FOLLOWING INTERNAL HEMORRHAGE

The next case I should like to consider is that of a 35 year old woman who came into the hospital with a history of three weeks of crampy lower abdominal pain and some vague vaginal spotting She had missed a menstrual period Although she was childless, she was interested in becoming pregnant Two hours before admission, she was suddenly seized with severe, generalized, abdominal pain, worst in the lower abdomen She felt nauseated, broke out in a sweat, did not vomit, had pain in both shoulders, was weak and nervous, and she stated that she was hungry for air

* Freeman, D S · *Lee's Lieutenants, A Study in Command* New York, Scribner, 1944

it through, although we had no evidence of elevated venous pressure in her Although her blood pressure, urine flow, and all the simple peripheral indices of her hemodynamic state were restored to normal, she never regained consciousness, and she died three days later At postmortem, she showed cerebral edema with a pressure cone.

SHOCK ACCOMPANYING OPERATIVE PROCEDURES IN A PATIENT WITH IMPAIRED ADRENAL CORTICAL FUNCTION

The sixth patient was a 62 year old woman with carcinoma of the anal canal It was clear clinically that she was going to require three operations one to remove the carcinoma and the others to get rid of the inguinal nodes which were involved Her first operation started out under poor auspices in that she developed hypotension under anesthesia She was transfused with only moderate success, and possibly without much wisdom The operation was continued and carried through She made a very slow and very precarious recovery from it, with amounts of blood transfusion far in excess of anything she had lost No diagnosis was made

The second operation was commenced, and as soon as her anesthesia started, she developed severe hypotension and went into warm shock We might call it "Dibenamine hypotension" At that time the surgeon stopped, and for the first time the lights began to flicker An eosinophil count was in the normal range, despite the fact that the mere induction of anesthesia should lower it practically to zero With this in mind, she was studied, and it was found that although she had no overt Addison's disease and no evidence of tuberculosis anywhere, let alone in her adrenals, she had some sort of functional adrenal insufficiency Her initial response to ACTH was subnormal She was given ACTH over a period of about ten days Her adrenal cortex was built up to a normal state of responsiveness She was then operated upon and went through her procedure without event

SHOCK ACCOMPANYING MASSIVE BOWEL GANGRENE

The seventh case is that of a woman in her mid-thirties who was pregnant with twins She went into labor and the twins were delivered but during labor she was seized with a terrific, tearing, agonizing abdominal pain It was felt at the time that she might possibly have ruptured the uterus, or that there might be some other calamity of an obstetrical nature, but this was not borne out by the findings on examination After delivery she continued to have abdominal pain, and developed abdominal distention and a silent abdomen with vomiting

this means he was given about 700 ml. of whole blood.

This blood was run in with the greatest of ease, rapidly and without much pressure. The patient rallied His pulse became obtainable, his blood pressure rose, and, to make a long story short, his arterial transfusion, whose possible effect we shall discuss in a minute, appeared to be the turning point

A question often asked is whether arterial transfusion should be given under pressure The answer is that if you have to use much pressure to give an arterial transfusion, the patient probably does not need it

SHOCK FOLLOWING TRAUMA WITH A HUGE HEMATOMA

The fourth patient was a 23 year old man who had been run over by a tractor He had a crushed pelvis, compound fractures of both femora, some external bleeding, and a huge retroperitoneal hematoma which could be palpated easily He had been injured in the country and was treated at a small hospital He was in shock for about twenty-four hours, by which I mean that he was hypotensive for that length of time When he came out of shock, he was still extremely ill, and the most outstanding fact was that he was anuric His anuria, or extreme oliguria, persisted He was admitted to our hospital four days later, and at that time he had already developed significant hypertension, it is relatively rare to develop the latter that rapidly

We did not know what was going on An electrocardiogram showed changes characteristic of potassium toxicity On admission, his potassium level was 7 4 milliequivalents per liter. (I should like to remind you again that this was only four days after the injury) This plasma potassium level rose throughout that day. On his way to be dialyzed on the artificial kidney, he died. At the time of death, his plasma potassium was 12 4

That is an example in which shock had been dealt with, but local tissue damage, namely, in the kidney, plus release of pigment and intracellular electrolytes, produced death

SHOCK FOLLOWING EXTERNAL HEMORRHAGE

The fifth case is that of a 32 year old psychotic woman who attempted suicide by cutting her throat The woman missed both arteries and the trachea, and cut both the major veins She had massive hemorrhage from her external jugular vein, and lay at home about six hours before she was brought to the hospital She was immediately treated with antibiotics and blood transfusion The blood transfusion was given on both sides of the circulation, both venous and arterial, because we felt that she might not be putting

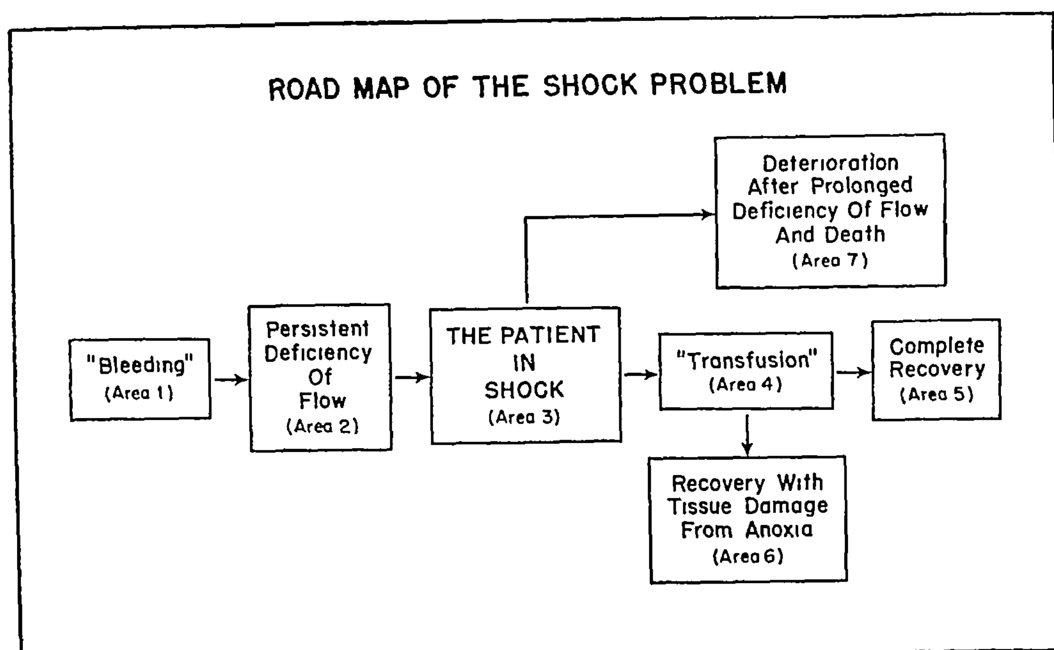


FIGURE 18

This was demonstrated in the case I mentioned of the young woman with the ruptured ectopic pregnancy Although we do not need to waste much time here, we should remind ourselves at frequent intervals that severe and apparently fatal shock, if of short duration, is readily susceptible to reversal by appropriate treatment Furthermore, the term "irreversible" should *never* be used in the clinic, since it is a defeatist's term A second outcome for the patient in shock is retransfusion and restoration of flow, only to suffer from the late effects of tissue anoxia in special organ systems This I have marked as Area 6 on the chart Examples are to be found in the nephrotic lesions which follow shock and are exemplified in the case of the boy crushed by a tractor It is also to be found in central nervous system damage following shock, as the attempted suicide who died of cerebral edema We have seen persistent jaundice as a manifestation of organ damage after shock

And finally, there is the third outcome, namely, death Here I like very much Dr Zweifach's phrase "deterioration after hypotension " In the shock problem, this seems to be the big area of research and controversy It is marked Area 7 on the chart This phase of shock has been the heart of the problem in the laboratory In discussing deterioration after prolonged deficiency of flow, we have concentrated on three mechanisms First, circulating humoral factors, which Dr Zweifach has studied, second, the overactivity of autonomic factors, which Dr Remington has studied, and third, the

At that point she was given antibiotics in tremendous doses, starting with penicillin and streptomycin, and then, within twelve hours, intravenous terramycin. Her abdominal situation progressed anatomically in such a way that it was clear that there was massive damage to her gastrointestinal tract. An exploratory operation, carried out within twenty-four hours of delivery, showed that most of her bowel was gangrenous, and that nothing could be done. She lived about three weeks longer. Antibiotics were continued. She never went into a shocklike state. She remained perfectly oriented, and sat up in bed in the morning reading the newspaper. There was a silent abdomen and leukocytosis but little other evidence of infection.

About two weeks after delivery, she was again operated on in the desperate hope that something might be done. To our amazement, we found that her entire gastrointestinal tract was not only black but had completely disintegrated. Cultures from the peritoneal cavity were absolutely sterile. She finally died, but she did not die of either shock or sepsis. She was an example, I think, of a patient in whom, just by chance, the spectrum of antibiotics given happened to hit all the organisms in her gastrointestinal tract, so that she could survive one of the most potent shock-producing stimuli we know, namely, massive bowel gangrene, without any systemic response whatsoever.

ROAD MAP OF SHOCK PROBLEM

Possibly these seven cases bring up a few of the things we have been talking about in the last two days, but under a clinical disguise. It might be useful now to go back and make a chart which could be called "A Road Map of the Shock Problem" (Figure 18). Sometimes this has been helpful in discussions of the subject. "Volume deficit in the vascular bed" goes on the left as being the primary etiologic factor. I am not sure but that I like Dr. Fine's definition better. He called it a persisting deficiency of flow.

Of course, we realize that this persistent deficiency in flow may be produced by whole blood loss, extracellular fluid loss, and so on, up and down the line, including, in certain instances, neurogenic factors as in primary syncope, and also postural and gravitation factors. The result of the persistent deficiency in flow is a patient in shock, marked as Area 3 on the chart. This is where the clinical problem lies and this is where the major military problem lies, exemplified as well as anything by Stonewall Jackson's death. The patient in shock then faces three possible outcomes. First, there is a retransfusion and complete recovery with no sequelae.

normal male adult total body water put the intracellular water around 40 per cent of body weight, rather than higher, as shown in the chart. But the principle is the same.

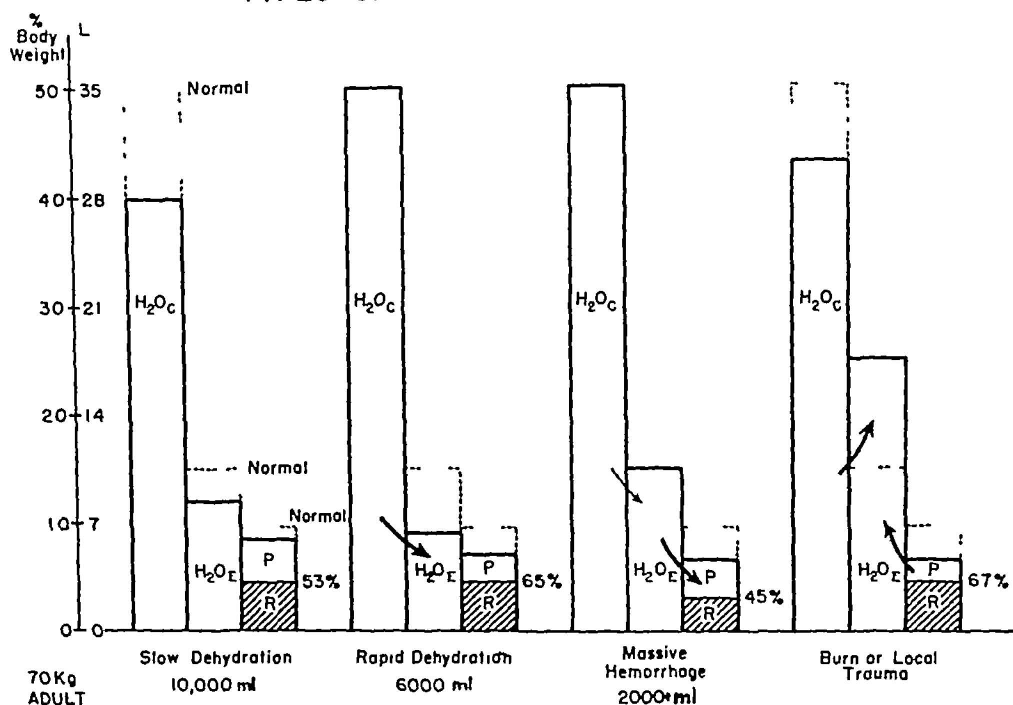


FIGURE 19 Types of Water Redistribution The heights of the columns are approximately proportional to the amount of water in cells (H_2O_C), extra interstitial fluid (H_2O_E), plasma (P), and red blood cells (R) See text for details The third column shows the events after hemorrhage, it is important to emphasize that refilling of the blood volume after hemorrhage comes almost entirely from interstitial water and that capillary permeability is the controlling factor in determining the rates of replacement and the substances which cross into the plasma volume This Figure has previously been published in *Symposium on Shock*, Army Medical Service Graduate School, Army Medical Center, Washington, D C

In slow dehydration, water is pulled out of all of these compartments proportionately as evidenced by negative potassium and sodium balance, commensurate with the water loss and negative nitrogen balance The production of shock by dehydration alone is not common but it does occur. However, as a stage setting for shock, dehydration can be very important We must all realize that when dehydration is in the background of shock it is of great and dire significance The renal lesion is more apt to develop, evidently, and there is much less body water for transcapillary refilling of the blood volume

Turning now to rapid dehydration, as for instance in intestinal obstruction, we find that water is removed out of the interstitial

occurrence of a special type of fatal infection in the presence of tissue anoxia, the mechanism of which Dr Fine has studied As I indicated in the opening of my discussion, all three of these remain high on the clinical priority list The clinician must study deterioration after prolonged deficiency of flow just as the experimentalist has, to discern whether any one of these three mechanisms is indeed responsible for death in the human being

In the laboratory, shock can be put together as a reasonably controlled and isolated phenomenon, although it is interesting what bitter discussions we have had in the last two days as to just how isolated some one preparation was.

Clinical shock in the living patient is almost impossible to deal with surgically or to consider physiologically without an understanding of the exact nature of the causative agent, (Area 1 on the chart) If the patient is in shock because of a ruptured spleen, the whole therapeutic approach is clearly going to be quite different from the patient in shock because of bilateral compound fractures of the femora The problems of clinical shock are not to be dismissed with the well-known aphorism that the first step in treating shock is to put a stop to the mechanisms which are causing it And yet, for purposes of brevity in this scientific discussion, I am not going to spend any more time in this fruitful clinical area

DISTRIBUTION OF WATER AND SOLUTES

However, I should like to spend some time in what we might call a primary problem, marked Area 3 on the chart, and known to us all as the patient in shock Again in the interest of brevity, and to strip things down to the core, I am not going to talk about blood substitutes for the very simple reason that I have had no experience with them and don't know anything about them Furthermore, I don't know of any substitute for whole blood, none has yet been manufactured containing hundreds of millions of little biconcave discs, 7 microns in diameter Until we manufacture such interesting fluid, we won't have anything that seriously competes with blood But I should like to spend a minute or two on the very interesting functions of this same red cell in the treatment of patients in shock An understanding of this has to do with the distribution of water and solutes in the various compartments of the body Figure 19 is a diagrammatic method of representation of the distribution of body water Per cent of body weight is used as an ordinate to express the weight of water inside cells, the weight of interstitial water, plasma water, and red cells On the chart, the values for intracellular water are rather high Our recent measurements of

rapid extracellular dehydration, as in intestinal obstruction, depletes the plasma and interstitial space more rapidly with a slow cell transfer Now, let us move on to the third example, namely, that of acute hemorrhage As we are all aware, right after the hemorrhage the hematocrit is normal It takes time for transcapillary refilling of the blood volume But, in general, that rate is rather rapid, and we have roughly quantitated it as being about 750 to 1000 ml in twenty-four hours in a normal adult male This should reduce the amount of fluid in the extracellular space outside of the blood stream We are not going to waste time on body fluid space measurement methods, yet I should point out to you that this lowering of interstitial fluid volume after hemorrhage, as a result of transcapillary restoration, has never been documented in the human, even though we are all confident that it occurs

Is there a transfer of water from cells in response to hemorrhage? The loss of potassium which follows hemorrhage is definite but

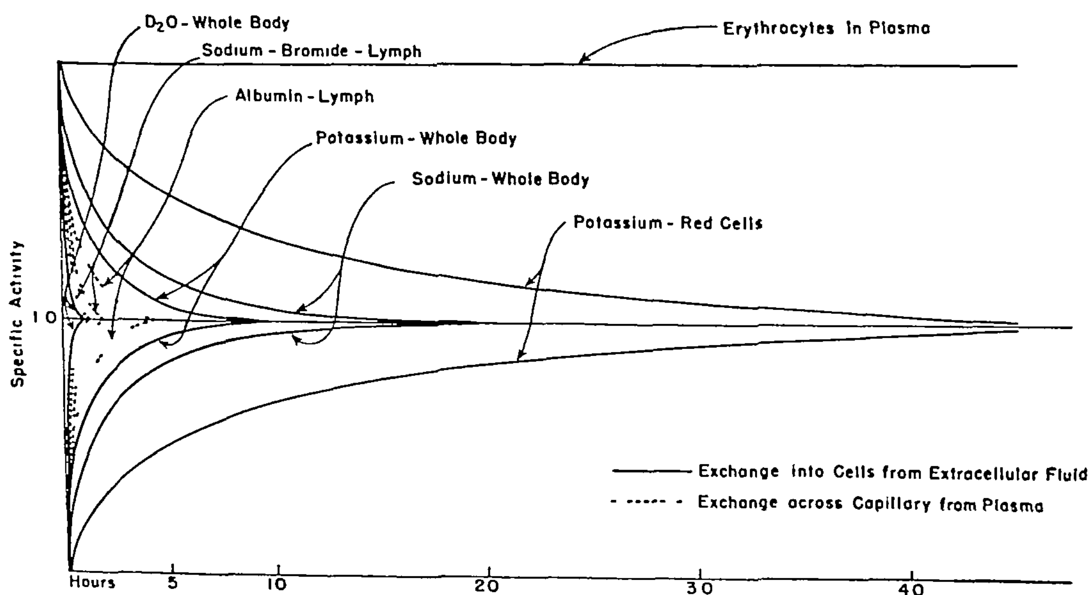


FIGURE 20 Permeability Spectrum The upper (falling) curves demonstrate diagrammatically the disappearance of various tracers from plasma The tracers used are radioactive or stable isotopes as inorganic ions or in appropriate organic configuration The rising (lower) curves demonstrate the increasing concentration of the tracers elsewhere in the body A specific activity of 1 0 indicates complete exchange across the body membrane involved The important point is that the curve for erythrocytes in plasma is essentially "flat" The space-filling contribution of the erythrocyte to blood volume is not lost by any normal permeability relationships It is only lost by frank external hemorrhage This Figure has previously been published in *Symposium on Shock*, Army Medical Service Graduate School, Army Medical Center, Washington, D C

and plasma area very rapidly and at tremendous volume expense, with only a very minor transfer of water from cells This is manifest metabolically by highly negative sodium balance, as much as 400 mEq per day, and negligible losses of potassium (possibly 70 or 80 a day) Plasma volume is greatly reduced, as has been measured by many investigators, especially by Dr. Fine's group many years ago And, of course, shock is produced by oligemia with a high hematocrit It is of interest that transfer of cell water does take place, but it cannot take place fast enough to keep up. If this situation is untreated and the patient does not succumb, the transfer of cell water does take place, and there is some restoration downward of the hematocrit, along with the continued strongly negative potassium balance, as evidence of loss of cell water

Nickerson· In that case you are referring to loss of a normal concentration of electrolytes as well as water?

Moore Yes, I am simply quoting the electrolyte balance as being at least a first approximation or estimate as to where the water has come from But the sodium loss is, generally speaking, at a concentration of 130 milliequivalents per liter or less

Nickerson The difference in equilibrium between that and the first case is presumably due to the fact that electrolytes are lost along with the water

Moore It is a question of rate The rate at which cell water can move into the extracellular spaces is slow, and dehydration has to be slow in order to pull water equally out of all compartments

Nickerson. The proportionate loss of water from all compartments is dependent upon a loss of water without electrolyte, as you have shown in your first example

Moore In the first phase one may, of course, occasionally find patients with high blood electrolyte value, if that is what you mean, who lose water preferentially from their lungs, for instance

Nickerson Yes If considerable amounts of extracellular electrolyte are lost, there is less tendency for water to leave the cellular compartment than when water is lost without electrolyte

Moore That is true, but a patient who is simply being dehydrated by insensible loss, if you will, will be in negative potassium balance

Nickerson. Yes

Moore To go back a bit, we have seen how slow dehydration pulls water out of all the body proportionately We have seen how

the whole body at slower rates, depending upon where they are going and which compartments of the body they are entering

For instance, notice that potassium equilibrium into the whole body takes place a lot faster than it does into the red cell To our surprise, we find that albumin apparently penetrates across the capillary into lymph at a rate which produces something approximating equilibrium in about three to five hours These data are based on studies of blood volume after the infusion of albumin and on disappearance curves of various types of tagged albumin and on the appearance of tagged albumin in lymph

These albumin curves make it important for us to realize —and I think this is inadequately emphasized — that almost half the plasma protein in the body is outside the plasma. I think it would be better to use the term "extracellular solute protein" rather than "plasma protein " I cannot seriously imagine anybody taking on that bulky term, but at least it is more descriptive The work on liver lymph, heart lymph, and visceral lymph tells us, at least in general, where a lot of this extravascular plasma protein is It is in the interstitial fluid of the parenchymatous viscera.

In doing tracer studies with albumin and cannulating the thoracic duct, one finds extremely rapid penetration, and, indeed, equilibrium of exchange seems to occur across the liver capillary with albumin almost as fast as it does with electrolytes One is dealing here, obviously, with a very special area in which the boundary between plasma and interstitial fluid is rather unusually permeable to albumin

The potassium and sodium curve I won't spend too much time on Dr Burch has done a lot of work on the body equilibrium of sodium I might just say that, if we were drawing this chart today, we would not draw it quite that way, since we know that a large fraction of the sodium in bone apparently does not exchange at all But that is another story

Let us dismiss all the curves we have looked at so far by saying that water, certain electrolytes, and albumin are given to wandering far afield and will leave the plasma, when placed there to restore plasma volume They will leave it to distribute themselves in their normal partition, and the volume-supporting effect is soon gone

In contrast to all these curves, look at the top curve of erythrocytes in plasma It is essentially flat Indeed, there was a time when the physicist maintained that it was absolutely flat Of course, it is not absolutely flat, but the only disappearance is due to the "biological decay rate" of hemoglobin The point is that tagged erythrocytes distribute themselves in the red cell mass and *stay there*

small If we assume that this potassium is being lost from cells with a commensurate amount of water, which may be an unjustified assumption, the data do suggest that there is a slow equilibrium across the cell membrane as well as across the capillary, tending gradually to restore water relationships to normal

The situation in a burn or local trauma is simply the accumulation of water from the blood stream and from cells in a special compartment of the interstitial fluid in the area of the trauma We might call this the "trauma edema" or "burn edema" We like to think of it as a parasitic or obligatory expansion of the interstitial phase

These transfers of water and solutes within the body in response to trauma, shock, hemorrhage, and dehydration are of significance to this Conference for two very important reasons First, we should not lose sight of volume redistributions within the organism which have survival value Secondly, and far more important, is the fact that water and solutes move freely across these membranes and when, in the presence of persistent volume deficit in the blood stream, we restore that volume only with water and solutes, these soon transfer themselves across the capillary and distribute themselves pro rata in body water, according to their electrolyte composition Indeed, we might state a general rule as follows *The usefulness of substances in the intravascular treatment of shock is an inverse function of the rate at which they can cross the capillary.*

RATE AT WHICH SUBSTANCES CROSS THE CAPILLARY MEMBRANE

Let us have a look at the rate at which some substances cross the capillary In Figure 20 is shown a diagrammatic representation of many studies done in our laboratories and elsewhere of the permeability of the capillary and of the total body membrane to various things placed in the plasma As we can readily see, the deuterium equilibrium into the whole body is extremely rapid We should remind ourselves that the mobility of tracer amounts does not argue that the mass transport of water takes place at that rate Indeed, we know that it does not and that the mass transport of water is a function of the permeability of the capillary or the cell, not only to the water itself but to the electrolytes, without which it will not move The deuterium data are purely of interest with respect to permeability to *water* itself

Sodium and bromide, which are the only two electrolytes we have studied — others have studied some other inorganic ions — cross the capillary with great rapidity and then equilibrate out into

the whole body at slower rates, depending upon where they are going and which compartments of the body they are entering

For instance, notice that potassium equilibrium into the whole body takes place a lot faster than it does into the red cell To our surprise, we find that albumin apparently penetrates across the capillary into lymph at a rate which produces something approximating equilibrium in about three to five hours These data are based on studies of blood volume after the infusion of albumin and on disappearance curves of various types of tagged albumin and on the appearance of tagged albumin in lymph

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From the point of view of the treatment of shock, the contrast of this curve with all of the others is the very heart of the problem And it summarizes what I have said about blood substitutes, namely, that there is no such thing. The erythrocyte has a space-occupying function which is unique. This space-occupying function is fully as important in the shock patient as is the oxygen-carrying, carbon-dioxide exchanging, and pH buffering effects of blood I believe it was one of the physical chemists who stated that the red blood cell was six hundred times as long and one billion times as heavy as the albumin molecule. That is a big difference, and that difference is responsible for the fact that when we put red blood cells into the blood stream they stay put. The red blood cell occupies space within the blood stream as long as the erythrocyte itself is not leaking out through an obvious external leak, known to us all as hemorrhage

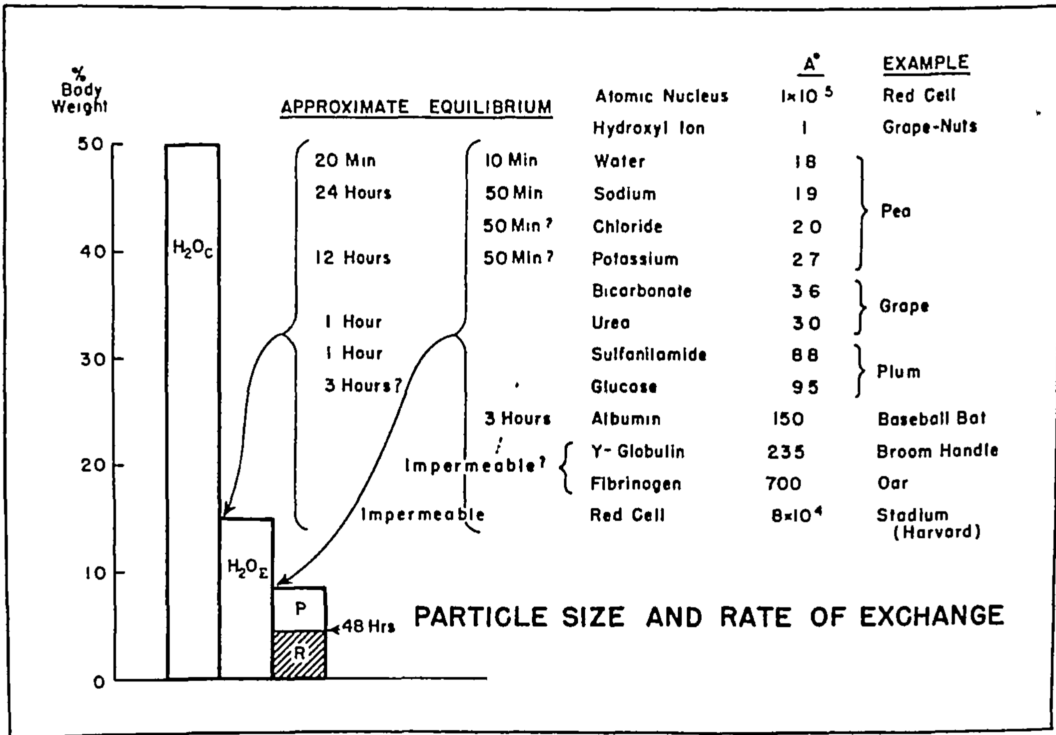


FIGURE 21 Particle Size and Rate of Exchange Approximate equilibrium times across the capillary and cell membrane are shown for a mixed group of ions, crystalloids, proteins, and the red cell. Particle size is roughly approximated in Angstrom units A size spectrum for comparison ranging from the red cell to a football stadium is also shown We are indebted to the physical chemist for much of these data and apologize for any inaccuracies The important point is that the red blood cell is of a dimension far removed from any of the other substances circulating in the blood and it is this huge size which gives to the erythrocyte its unique space-occupying property in the blood volume This Figure has previously been published in *Symposium on Shock*, Army Medical Service Graduate School, Army Medical Center, Washington, D C

In Figure 21 we see another way of looking at some of these things This is a simplified diagram, showing molecular dimensions in Ångstroms I am indebted entirely to the physical chemists for these data Some of these data are probably obsolete and will be revised because of water of hydration or some other factor The point is that the red cell is so huge that it restores volume deficit and corrects a persistent deficiency in flow in a manner more lasting than any of the other substances

During the last war, Dr Richards (1) studied some human patients in shock and showed the blood volume increment per ml of therapeutic fluid infused If I remember his figures correctly, he showed that in shock there was a blood volume increment of only 0 1 ml per milliliter of saline solution infused I don't fully understand this, as we would expect the increment to be slightly larger

Albumin was shown to produce a 30 per cent increment In other words, for each milliliter infused, 0.3 ml was retained in the blood stream

Whole blood had a 60 per cent volume increment We might call it a 60 per cent dividend on the investment For each milliliter infused, 0 6 ml remained in the blood stream The difference between albumin and whole blood was wholly due to the space-occupying function of the red cell mass

I would summarize what I have said so far by the statement that the patient in clinical shock must be approached with the causative agent in mind and is best treated with whole blood because whole blood contains suspended in it the red cell which stays where it is put

Moving from these considerations over to Area 7 on our road map, I am going to take a back seat We have spent a good deal of time talking about deterioration after prolonged deficiency of flow I should like to raise the point that we must differentiate with great care between the etiology of deterioration and the effects of deterioration That has worried me somewhat in the problem of VDM and of secondary bacterial infection Are these the result of tissue anoxia or are they the cause of further tissue anoxia, or both?

The teleology of the autonomic nervous system has been brought up by Dr Remington, and I think we are going to be hearing a lot more about it Some years ago shock was produced experimentally by prolonged intravenous injection of epinephrine This appeared to be grossly in contradiction to the classical concept that adrenal medullary discharge protected the organism Now it is interesting

to find that Dibenamine can, under certain special circumstances, protect the organism. Maybe we are dealing with a response which has survival value but which becomes deleterious when it "overshoots"

Clinically, we have all recognized for years that warm, dry, pink shock or hypotension is a much more benign situation than cold, wet, clammy shock or hypotension In fact, the former possibly should not be referred to as shock at all Recent work in England is interesting in this connection because total spinal anesthesia has been produced, giving rise to a persistent low blood pressure and, of course, a vasodilated periphery Prolonged surgical operations have been carried out under these circumstances with very little bleeding and no tissue damage It certainly would be helpful if somebody here would discuss tissue oxygenation in the presence of well-oxygenated blood flowing slowly with a low peripheral resistance and a low central pressure

RENAL ISCHEMIA ASSOCIATED EFFECT OF PIGMENT EXCRETION

Let us turn now to Area 6 of our road map, namely, special organ damage In some work which we are now doing in the laboratory and which has been carried out by Drs Chester Rosoff, Robert Weiner, Robert Desautels, and Carl Walter (2,3) of our service, the kidneys of dogs have been explanted into the flanks, and a snare has been put around one or both renal arteries It is thus possible to produce unilateral or bilateral renal ischemia During ischemia, we inject methemoglobin into the dog and can produce either a unilateral or a bilateral tubular lesion by the combination of renal ischemia plus the pigment We have confirmed the work of others that the pigment alone does not damage the kidney, and the renal ischemia does not damage the kidney either, if its duration is not too great

The tubular lesion which is produced is a very extensive one microscopically, and there is good resemblance to the human lesion If bilateral, uremia, elevated plasma potassium concentration, and death will occur The beauty of the preparation, however, is that it can be produced unilaterally, so that the opposite kidney takes care of the dog and lets the sick kidney get well With the kidney explanted into the flank, we can follow the chemical changes in the urine and the histologic changes of renal healing by frequent biopsy We have concluded from this, as others have suspected from clinical work, that this nephrotic lesion, or whatever we want to call it, which is killing a great many people now and is a tre-

mendous problem in military surgery, is a lesion which has an intrinsic tendency to heal It will heal rapidly and heal completely with almost no residual effects if the total organism can be kept alive long enough to let it heal Therein of course lies the value of such mechanisms as peritoneal lavage and the artificial kidney in treating a post-traumatic renal lesion

This renal lesion has been called "lower nephron nephrosis" I prefer to call it "ischemic pigment nephrosis," to demonstrate the fact that both ischemia and pigment are required to produce it. In the clinical patient, the ischemia arises from shock or shocklike states The pigment may come from many sources from transfused blood, from crushed muscle, from the liver, in the form of bile pigment, or, more particularly, from the simple breakdown of tissue hematomas, as in a fracture

One of our problems is Does differential renal vasoconstriction in response to blood volume deficit set the stage for this lesion? Is such renal vasoconstriction a function of adrenomedullary discharge? I don't know the answer If it is, there is another reason for looking at Dibenamine with great interest

Bradley What do you mean by differential renal vasoconstriction?

Moore I mean a vasoconstriction in the kidney which is out of proportion to the vasoconstriction in the rest of the peripheral vascular bed A patient is injured and goes into shock or a shock-like state, with a prolonged period of oliguria or anuria Is such diminution in renal output due to renal vasoconstriction resulting from epinephrine or any of its relatives? That question I would have answered two or three years ago by saying, "Of course, it must be" But I am not so sure now that that is true

Selkurt Are you inferring that it is sustained renal vasoconstriction, or some real pathological change in the vasculature? As far as the persistent vasoconstriction, that should vanish rather soon

Moore The persistent oliguria may not be evidence of continuing vasoconstriction, particularly if pigment has been released, but I think the evidence suggests that the early changes, within the first few hours, are due to vasoconstriction

Bradley Isn't there evidence that the blood flow through the kidney is diminished for a long period of time after the initial trauma?

Selkurt Consider the data of Lauson and associates (4) in which the renal artery of the dog was clamped for two hours Extraction ratios for p-aminohippurate, related to clearance, showed that the plasma flow returned very soon, but that the tubular effects went

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on for days

Bradley Both Bull (5), in London, and Sirota (6), in New York, state that the blood flow through the kidney is greatly reduced for periods of several weeks after the initial injury. Tubular extraction of PAH is also greatly reduced, but even when the clearances are corrected for this defect the renal blood flow is reduced

Stead There is just one clinical point on which I should want to change your diagram, and that is while deterioration after hypotension may be, in certain instances, due to infection and the products thereof, in many instances cellular deterioration occurs before circulatory failure There isn't any hypertension with the infection I think you have to put it as a primary initiating factor, as well as being initiated secondary to circulatory failure

Moore Do I understand you to mean that acute infection can produce the whole picture of shock by replacing bleeding away back in Area 1 of the chart?

Stead. Yes I don't think it concerns the vascular deficit I personally don't think it is a volume deficit in the vascular bed

Moore I don't know.

Stead I should have wanted other primary things, if you are going to get into the clinical picture of shock, besides blood volume and hemodynamic differences

Moore: Certainly, infection may be a factor in initiating shock in clinical patients The reason I told about the patient with the gangrenous bowel was that she constitutes an example where shock, which we had every reason to expect, was evidently prevented completely by sterilizing the contents of the intestinal tract As I said before, Dr Fine's work must fill all of us with a desire to return to clinical patients and do more careful cultures in shock

Stead The patient begins to get sick in the beginning when infection starts the process, and the patient ends in circulatory failure.

Moore: But you don't think the shock is due to any vascular deficiency?

Stead: I think the patient gets sick, not that it is a volume defect in the vascular bed I think this is sickness of the cells

Moore In other words, you would like to use Dr Fine's term of deficiency of flow, whether or not there was a volume deficiency?

Stead: Yes.

Moore I certainly go along with you on that I think it is a much more inclusive term

Green In Rickettsial diseases, George Harrell (7) felt it was

primarily a volume loss, didn't he?

Stead: It is certainly true that in all of these things, when you are dealing with sick people, you can get secondary effects and minor effects, but the practical fact is that given a man with progressive infection, no one has ever appreciably modified the clinical picture by doing anything to the blood volume When you get these people well, it is by keeping your eye on one thing and that is getting rid of the infection. In other words, if you take a Rickettsial disease and treat it with aureomycin and chloromycetin, recovery occurs rapidly. If you treat the patient primarily with blood and plasma, the mortality rate is changed very little

Moore: If renal vasoconstriction on the basis of epinephrine makes the kidney vulnerable to pigment damage, then this constitutes another area which we must study clinically from the point of view of a trial of Dibenamine The combination of shock plus pigment producing a nephrotic lesion is, of course, a common and familiar one. The reason I told about the man who had been run over by the tractor was that he showed this combination of renal ischemia plus pigment His pigment came, of course, from his huge retroperitoneal hematoma There was a lot of whole blood there which was breaking down in the tissue of his retroperitoneal area After a period of shock, with this pigment circulating, he developed renal shutdown, which ultimately killed him. If we could interfere with the early renal vasoconstriction by means of a blocking agent so that the kidney of the injured patient is not vulnerable to pigment, we certainly would move ahead

Franklin I know of a case where the renal cortical vessels were shown to be constricted during life It was an obstetrical case, with concealed accidental hemorrhage A biopsy performed the day after the patient's admission showed that the renal cortex was ischemic, but that blood continued to circulate through the medulla (8)

Moore· And the kidneys in this particular patient showed cortical ischemia? Was it the sort of ischemia which you would suspect might lead later to the development of a bilateral nephrosis?

Franklin She went on living for about a week, and at postmortem they found renal cortical necrosis

Moore If I am not mistaken, that particular complication of going on to frank nephrosis is more common in the obstetrical cases Whether it is a qualitatively different thing from that which we are talking about in shock or the same thing carried to a greater extent, I don't know

Nickerson I am sure that a great variety of factors may cause

on for days

Bradley. Both Bull (5), in London, and Sirota (6), in New York, state that the blood flow through the kidney is greatly reduced for periods of several weeks after the initial injury. Tubular extraction of PAH is also greatly reduced, but even when the clearances are corrected for this defect the renal blood flow is reduced

Stead There is just one clinical point on which I should want to change your diagram, and that is while deterioration after hypotension may be, in certain instances, due to infection and the products thereof, in many instances cellular deterioration occurs before circulatory failure There isn't any hypertension with the infection I think you have to put it as a primary initiating factor, as well as being initiated secondary to circulatory failure

Moore Do I understand you to mean that acute infection can produce the whole picture of shock by replacing bleeding away back in Area 1 of the chart?

Stead Yes I don't think it concerns the vascular deficit I personally don't think it is a volume deficit in the vascular bed

Moore I don't know

Stead I should have wanted other primary things, if you are going to get into the clinical picture of shock, besides blood volume and hemodynamic differences

Moore Certainly, infection may be a factor in initiating shock in clinical patients The reason I told about the patient with the gangrenous bowel was that she constitutes an example where shock, which we had every reason to expect, was evidently prevented completely by sterilizing the contents of the intestinal tract As I said before, Dr Fine's work must fill all of us with a desire to return to clinical patients and do more careful cultures in shock

Stead· The patient begins to get sick in the beginning when infection starts the process, and the patient ends in circulatory failure

Moore: But you don't think the shock is due to any vascular deficiency?

Stead I think the patient gets sick, not that it is a volume defect in the vascular bed I think this is sickness of the cells

Moore In other words, you would like to use Dr Fine's term of deficiency of flow, whether or not there was a volume deficiency?

Stead· Yes

Moore I certainly go along with you on that I think it is a much more inclusive term

Green In Rickettsial diseases, George Harrell (7) felt it was

primarily a volume loss, didn't he?

Stead. It is certainly true that in all of these things, when you are dealing with sick people, you can get secondary effects and minor effects, but the practical fact is that given a man with progressive infection, no one has ever appreciably modified the clinical picture by doing anything to the blood volume When you get these people well, it is by keeping your eye on one thing and that is getting rid of the infection In other words, if you take a Rickettsial disease and treat it with aureomycin and chloromycetin, recovery occurs rapidly If you treat the patient primarily with blood and plasma, the mortality rate is changed very little

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Nickerson I am sure that a great variety of factors may cause

renal shutdown However, I have seen two or three cases which appear to demonstrate rather clearly a sympatho-adrenal factor These were all cases of elderly people with an acute anuria following cystoscopy Such cases are notoriously unpredictable in that the kidney may open up suddenly without any treatment However, in each of these cases, there was a very close correlation between the administration of Dibenamine or 688A and the resumption of urine flow, so that I strongly tend to relate causally the administration of Dibenamine and the relief of anuria

Moore In the surgical cases that we have studied – and we have seen a great many of these patients because of the presence of the artificial kidney – the combination of renal ischemia, usually due to shock, plus a pigment, has nearly always been present Of course, that was the obvious reason for doing the experimental work that I mentioned I don't know how to get rid of the pigment I don't know how it can be dealt with But in view of the fact that the pigment alone without the renal ischemia does not seem to do much damage, I am led to believe that if you could take care of the renal ischemia, you might move on with this problem

Nickerson Additional cases should be studied with Dibenamine because the numbers to date are inadequate to allow any definite conclusions However, they are certainly suggestive.

Bradley. It should be pointed out that renal ischemia is not necessarily a result of renal vasoconstriction Certainly late in the shock syndrome and during the days that follow the recovery from shock, when oliguria or anuria may persist, edema of the kidney may play a role in reducing blood flow It is possible that the residual mass of functioning tissue is adequately perfused with blood even under these circumstances

Moore Would you agree, though, that a patient can have his renal ischemia for a fairly short time and if he at that time also is presented with a porphyrin pigment in his extracellular phase, he can then develop the renal lesion, and a day or two later be oliguric with no further discernible evidence as to why the kidney should be ischemic? The damage has been done and he remains oliguric

Bradley There is the problem It is often stated, or at least implied, that release of renal vasconstriction may be beneficial in the therapy of so-called "lower nephron nephrosis" But the data, such as that offered by Bull (5) and Sirota (6), indicate that the return of renal blood flow to normal values may be long delayed Diuresis, on the other hand, often occurs dramatically at a time when renal blood flow and glomerular filtration are greatly reduced. Hence,

the correction of the disturbance in urine formation appears to depend upon readjustment of tubular function In this view, an attempt to increase blood flow would be of little value It is still possible, of course, that a slight increment in filtration even at low levels may lead to re-establishment of a more nearly normal glomerular tubular balance and thus prove beneficial

Moore Definitely It is due to healing of a tubular lesion which had been produced previously by, at least to our way of thinking, a combination of ischemia plus pigment

Nickerson The cases to which I referred were, as far as I know, never in an actual state of shock, but I believe they point up the fact that the anuria can be on a strictly neurogenic basis This was demonstrated years ago by the observation that tying one ureter will cause contralateral renal vasoconstriction

Sharpey-Schafer The practical problem is what to do when the case is discovered after injury We saw a great many of these cases during the war, of course, in London The only portion of the body accessible may be the head You can't get to any other part of the body You might be able to inject something, like Dibenamine, that might save him What we did, of course, was to give him as much fluid as we could Some undoubtedly passed enough pigment that one would have suspected they would succumb, and they did seem to recover

Moore I think the therapeutic daydream here concerns the patient in shock with a pigment being released This pigment may be released as a result of muscle trauma or a big interstitial hematoma, it may be due to a mismatched transfusion, or to multiple, closely spaced transfusions without frank incompatibility, which may result in rather large amounts of hemoglobin release The hope is that such a patient, given adequate blood replacement, might at the same time be given a blocking agent so that he will not have this apparent renal ischemia while he is trying to deal with the pigment

Sharpey-Schafer They do not go into shock until they release the pigment

Fine Would you interpret what you think happens as a result of giving so much fluid?

Sharpey-Schafer I don't know When you get them out of shock, they have a large water diuresis going on Whether they get rid of just enough pigment, I don't know You immediately transfuse them You don't let them develop a low blood pressure state, and I think you protect them from the shut down in the kidney They

renal shutdown However, I have seen two or three cases which appear to demonstrate rather clearly a sympatho-adrenal factor. These were all cases of elderly people with an acute anuria following cystoscopy Such cases are notoriously unpredictable in that the kidney may open up suddenly without any treatment However, in each of these cases, there was a very close correlation between the administration of Dibenamine or 688A and the resumption of urine flow, so that I strongly tend to relate causally the administration of Dibenamine and the relief of anuria

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on the venous side, and fails to respond by a return of forward output and blood pressure to normal, one may suspect myocardial ischemia When clinical or laboratory evidence of an elevated venous pressure corroborates the impression, it is reasonable to try arterial transfusion The spectacular point is that when arterial transfusion is given in such cases, one not infrequently sees a dramatic clinical response to the infusion of only 500 ml, or so, of blood Is this improvement due to the fact that the arterial transfusion has perfused the coronary so that the myocardium can work well, take up the venous blood being presented to the right heart, and put it through with an adequate aortic pressure so that coronary flow is resumed on its own power? I put that in the form of a question because I don't know the answer

Shorr How does the time interval for an arterial transfusion compare with that in which a venous transfusion is given?

Moore We have seen patients, and I am sure many others have also, in whom venous transfusions were run in rapidly under pressure without much effect except to increase bleeding from veins in the operative site. When a much smaller quantity of blood is now run in on the arterial side, a clinical improvement occurs It is important to realize that the major arteries of the body form a unicameral system, and that pressure introduced at any point is communicated throughout the system Somebody always asks if the catheter has to point back towards the heart It does not make any difference, I am sure, since the newly introduced blood increases the pressure throughout the arterial tree I am sure that we have given inadequate attention to the coronary terminal vascular bed as being a terminal vascular bed involved in shock and undergoing changes which are detrimental to the heart muscle

Shorr Page has demonstrated the retrograde movement of the blood in the arterial tree

Bradley How long does it take to give an arterial transfusion? Would you not expect the coronary flow to be improved only during the time of transfusion?

Moore That is correct, only during the time of transfusion, and during the very short period in which the pressure is artificially maintained But if the heart muscle gets in a few good licks during that short time, then forward output is resumed and coronary flow is picked up

Burch You don't think it might be cerebral in origin?

Moore We have, of course, considered that but have no evidence one way or another

laboratoıs, which I mentioned above, tubular necrosis of massive character has often been seen without much precipitation of pigment in the tubule Indeed, in the clinical treatment of postshock anuria, it is of the greatest importance not to force water beyond the requirements of insensible or extrarenal losses As we all know, it is very easy to push these patients over into pulmonary edema, and they will live much longer if water, and particularly salt, are used with great care and caution

Stead· Just as a historical note, it might be worth remembering that it was not very long ago that the pathologists said these kidneys were all right When I was an intern, I can remember that when people died in this syndrome, the pathologists all said, "Pretty good-looking kidney." It is now interesting to know that they are getting better than we in telling the damage

Bradley I should like to know what the percentage is in civilian hospital autopsies

Nelson. It is proportional to the people who are looking for it

Moore It is also proportional to what sort of civilian population you are dealing with

MYOCARDIAL ISCHEMIA. INTRA-ARTERIAL TRANSFUSIONS

Bradley Dr Jean Oliver has observed these tubular lesions frequently in patients who die of heart failure

Moore Of course, these civilian patients with heart failure are much more apt to have pre-existent renal disease, which evidently makes the kidney much more liable to acute injury Certainly that is true in burns

There are only two other things which I planned to mention One of them has to do with arterial transfusion, the effects of which are at times dramatic That is the reason I mentioned the particular case history of the man with the extensive pelvic cancer who was unresponsive to intravenous transfusion I do not understand fully why patients are so reactive to arterial transfusion, unless it can be that the coronary artery is perfused when we give an arterial transfusion We are apt to forget that the coronary blood supply is a terminal vascular bed, in the sense of Dr Zweifach's work, and that when the terminal vascular bed as a whole is involved in the pathologic changes of shock, the myocardium is suffering along with tissues everywhere else in the body When the myocardium is so affected, it seems to me that a form of heart failure is produced, if you want to use that term, and I must admit that I use it with great fear and trepidation

When a patient has been given apparently adequate transfusion

of people who have tried this in the acute myocardial infarct, but I do not know of anybody who as yet has had a dramatically successful patient. There are a number of surgical patients who have profited by arterial transfusion

Bradley Is there any solid basis for believing that arterial transfusion does something that the venous transfusion does not do? Isn't this a clinical impression?

Howard To this extent Time and time again surgeons have reached the point where they have given eight or ten transfusions and the patient remains in profound hypotension, whereupon they transfer the needle, at the same rate of transfusion, into the artery, and immediately the hypotension and signs of shock rapidly diminish

Fine I think we ought to be clear about what Page intended to do by arterial transfusion (10) It is not a means for treating shock One is treating failure of the coronary circulation by use of this pressure infusion on the arterial side of the circulation There may be secondary shock because of failure of the heart But arterial transfusion is not intended to treat the peripheral vascular circulation, only the coronary circulation

Moore Wouldn't you agree that you have to go one step further and say that if a patient has benefited by an intra-arterial transfusion, as Dr Howard says, that patient, of course, needs to have his total blood volume deficit made up by one means or another, whether on the arterial or venous side?

Fine The patient, unfortunately, may even have a lesion in the coronary If you keep on giving blood into the veins, you may kill that individual That is where the error has been I can cite a case, such as the one Dr Howard just quoted, of a woman, who, I am sure, got a good deal more blood than her volume deficiency required, with no effect whatsoever on her shock state Then, after two days, it dawned on somebody that her shock was due to subacute left ventricular failure, and she was given an arterial transfusion After she had gotten arterial blood, she woke up, her blood pressure returned, the urinary function appeared, she had a warm, dry skin, and she was out of shock

Bradley Is that a clinical impression?

Fine No, that is not a clinical impression

Sharpey-Schafer If you raise the venous pressure by a venous transfusion to above normal, and there is no increase in output of the heart, and you transfer to the artery and get a striking increase in cardiac output, then there is —

Nickerson: There appears to be one other possibility. Even with a transient increase in pressure on the arterial side, vasospastic reflexes from the carotid sinus, aortic arch, and the like, may be reduced. This would relax peripheral constriction, allow blood to pass more readily between the arterial and venous sides, and perhaps set up a cycle of improved peripheral circulation, which could then be self-perpetuating.

Moore: That is an interesting thought.

Green: How much are you able to elevate the arterial pressure?

Moore: We have never measured that with an intra-arterial apparatus, so we cannot answer the question.

Selkurt: There is another fact concerning the coronary circulation which might have a bearing. Opdyke (9) in our department showed some time ago that the coronary bed was potentially dilated in shock, in the sense that, if more blood were made available, an increase in flow over that observed during the shock (hypotensive) state could be expected. So it seems to me that if you begin to boost blood flow through the coronary vessels, it is going to replenish the myocardium with oxygen, and that the volume of blood flow obtained will be beyond the volume which would perfuse the heart vessels at shock pressure levels.

Fremont-Smith: How long does an arterial transfusion last?

Moore: It depends upon how much you put in and how fast you do it. The particular one I mentioned takes only eight minutes.

Howard: Frequently, three or four minutes per 500 ml.

Green: Would you feel justified in doing simultaneous venesection to avoid overloading the heart from the venous side?

Moore: I suppose you might reasonably do it. If our theory is right, the heart does away with that by rapidly taking hold of the increased venous return.

Green: Suppose that it looked as if the heart were going to get started but then the venous pressure rose excessively as the result of the infusion of a large volume of blood? Would you then feel that venesection might be desirable?

Moore: We have venesected some persons after shock, but for the reason that they were overtransfused.

Fine: Dr. Stead, isn't that the sort of thing you might like to do in shock due to myocardial infarction – take blood out on the right side and put it in on the left side of the circulation.

Stead: Yes, but the difficulty comes in that you usually have too much muscle which is ischemic because of vascular disease and not secondary to the drop in arterial pressure. There are a number

us back all the way from the clinical cases we have been considering to the fundamental problem of hemodynamics, but it seems to me that it will illuminate this question of arterial transfusion against venous transfusion To get at the central problem of hemodynamics, we must ask, what is the relationship between pressure and flow? You see, that is intimately concerned We are always talking about the effects of hypotension Now, how many of these sequelae can we attribute to the low pressure?

Obviously, the first thing we must realize is that the driving pressure is low and the flow is less Now, what is the relation between pressure and flow? Can we generalize from vascular beds? If they were rigid tubes, we know, by Poiseuille's law, what the flow and pressure relations would be There is a long history of research by Whitaker and Winton and Green (14), and so on, showing that these ideal relations between flow and pressure were not the case in actual perfused vascular beds

We approached the matter from another direction We studied the theoretical basis of the stability of cylindrical vessels The vessel tends to be unstable and to close down or to dilate to its maximum when the pressure changes or when the tension in the wall changes As is true of every elastic tissue, which automatically changes the tension when it changes its size, this stability can be modified so that there can be a range of stability But even with elastic tissue in the vascular system, which possesses tone in its wall, which we call active tension and which can be changed by pressor substances or by neurogenic factors, there is still only a limited range of stability If the tension increases above a certain value, or the pressure falls below a certain value, the vessel will tend to close completely. This prediction is not controvertible from the physics, but, of course, the "critical closing pressure," as we call it, might be only a millimeter of mercury and have no theoretical significance

So in the last four or five years our group has been studying pressure-flow curves in the rabbit's leg and in the rabbit's ear, and now we have used the human arm We feel we have enough pressure-flow curves, with careful attention to what happens at the bottom, to generalize When the vessel is dilated, one gets a straight line which, however looks as though it does not quite hit the origin Actually it turns a bit and intercepts the pressure axis at a critical closing pressure which is never below 5 mm. Hg. As the vasomotor tone in the vessel is increased, the curves go through the following sequence They always start off at high pressure, pointing toward the origin, then they curve in, and in this range are sigmoid and

Fine. Decline in venous tension, which is what happened in this patient

Moore And it is what happened in the patient that I just mentioned I think the answer to Dr Bradley's question might be, "yes, it is a clinical impression."

Fine· It is very dramatic.

Moore It is a pretty forceful one It should be checked in the laboratory

Burch. I should like to know whether or not you attribute improvement to coronary flow or cerebral blood flow?

Fine The patient was not suffering from any cerebral symptom

Burch Criteria of the state of cerebral flow are not very reliable at times

Nickerson The picture presented by Dr Moore is one of venous engorgement and a very marked constriction of arteries and arterioles We know that in response to a transient increase in arterial pressure, the classical vasoregulatory reflexes will dilate the arterioles in a matter of seconds

Moore. When the arterial pressure is zero or near there, you certainly cannot accuse the left ventricle of having to work against too high a head of pressure

Nickerson Under those circumstances, the left ventricle obviously is not performing much work

Nelson The Russian literature contains some interesting experiences with intra-arterial transfusions (11) At an aid station in the battle of Stalingrad, Negovsky (12) instituted resuscitative measures of tracheal intubation and arterial transfusion in ten casualties said to be clinically dead Of these, five were returned to duty Langendorff (13) in 1895 observed that a freshly extirpated mammalian heart suspended in air at room temperature resumed full contractions when the stump of the aorta was perfused with saline under pressure By virtue of the direct perfusion of the heart via the coronaries, the transfusion of blood by artery seems logical in states of *profound* shock

Moore Mr Chairman, would it be all right to say that the group makes the statement that it is a strong clinical impression that arterial transfusion is a useful thing, and that it is in the area of supposition as to why it is useful? Maybe it is the coronary, maybe it is something else

Shorr I think most of us would agree with that statement

RELATIONSHIP OF FLOW TO PRESSURE

Burton I have been itching to give sort of a lecture It will take

us back all the way from the clinical cases we have been considering to the fundamental problem of hemodynamics, but it seems to me that it will illuminate this question of arterial transfusion against venous transfusion To get at the central problem of hemodynamics, we must ask, what is the relationship between pressure and flow? You see, that is intimately concerned We are always talking about the effects of hypotension Now, how many of these sequelae can we attribute to the low pressure?

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definitely intercept the pressure axis at a very great closing pressure, which may go up to 50 mm. Hg. The important thing is that the flow has a fantastic sensitivity to the pressure when vessels are under vasomotor tone. In the human arm, for instance, the critical closing pressure may be about 65 mm Hg If the vessels are dilated the curves may intercept the pressure axis as low as 15 mm. Hg If the subject is under high vasomotor tone, the shape of that curve is such that when the critical closing pressure is 70, a drop of blood pressure of 20 mm from a mean of 100 will result in a decrease of flow in that arm, which may go to one-fifth of what it was before, i e, a 20 per cent drop in blood pressure reduces the blood flow to one-fifth

One conclusion that we can draw, therefore, is that a change in blood pressure by transfusion, raising it under high tone, may produce an increase of flow in different vascular beds which is out of all proportion to what we would have thought from the classical view

The second conclusion is that the level of the blood pressure determines the effectiveness of the vasomotor impulses in controlling the circulation You can analyze curves the other way and see what happens with different frequencies of stimulation at a given pressure, and then what would happen for those same frequencies if the pressure were lowered You would find inevitably that a rate of stimulation of the sympathetic of, say, 5 or 10 a second, when the mean blood pressure is 100, might reduce the flow to one-half, but if that same blood pressure were lowered to 80, that same amount of stimulation in the sympathetic would reduce the flow to perhaps 10 per cent or to nothing at all So that, to me, gives a new importance per se to the level of the blood pressure in that when the blood pressure is a bit lower than normal, activity of the sympathetic is tremendously more effective in producing ischemia than when the blood pressure is normal

I might just add that my interpretation of what happens in shock when the kidney closes down is that under the condition of shock with high vasomotor tone, the critical closing pressure in the kidney is 70 mm Hg If the blood pressure falls below that, there is no flow

Selkurt. We have investigated that point, and it does not work that way in the kidney So we differ with you on that

Burton: I have not investigated the kidney, and so I don't know

Selkurt. To consider an analogous diagram for the kidney, showing the *pressure-flow* relationship (Figure 22), the normal curve

usually intercepts the pressure axis at about 10 mm. Hg, and is usually concave in shape (see left of Figure 22) When the kidney has a high degree of vasomotor tone, the relationship is more linear and flow is less at any given pressure, but it intercepts at about the same point (see right of Figure 22)

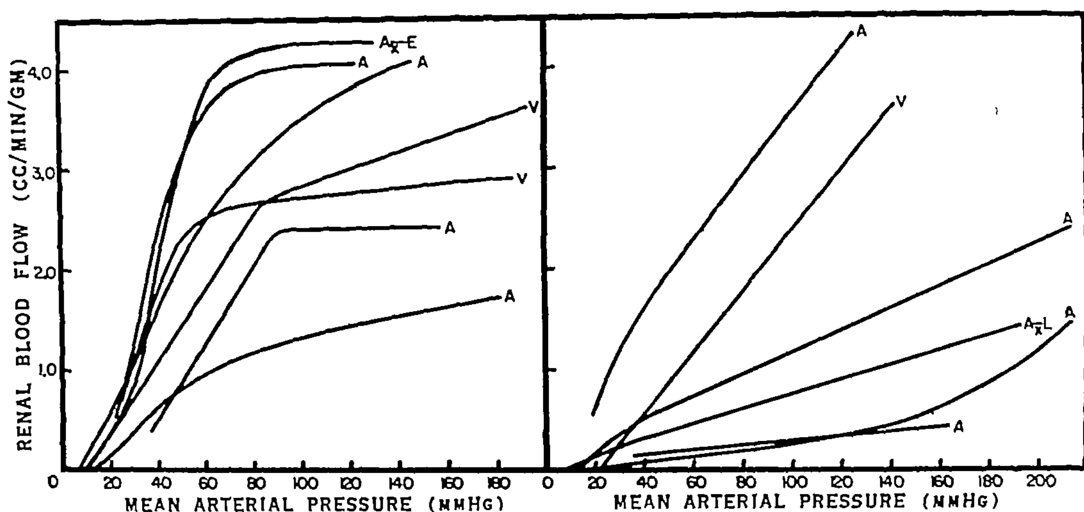


FIGURE 22 Pressure-flow relationship in the intact dog kidney, flow measured with rotameter under pentobarbital anesthesia Typical control curves to left, showing concavity To right, curves more typical of high resistance kidneys *A*, arterial inflow measure, *V* venous outflow measured A_x-E curve done early, and A_x-L, curve done late in the day in the same animal. Curves are extended to zero flow intercept only when values were actually measured Reprinted, by permission, from Ritter, E R Pressure-flow relations in the kidney Alleged effects of pulse pressure *Am J Physiol* (In press)

Moore That is total flow through the total kidney?

Selkurt Yes

Burch The situation may be different for the arm of man using the plethysmographic venous occlusive method for measuring flow If the hand and arm are cold, the venous reservoir for trapping the blood, of course, is reduced and thereby interferes with the accuracy of the method

Green I would thoroughly agree with what Dr Burton said, except that I do not think it applies to the heart because I have never seen this critical closing pressure in the heart go up appreciably in any condition resembling shock On the other hand, it is true that the critical closing pressure in the coronary circulation is above zero It is somewhere between 15 and 20 millimeters I don't think it goes up to those very high values

Burton I think Dr Selkurt showed 20 millimeters

Selkurt. In our original data it averaged about 14 mm Hg We have since repeated that study and corrected for the venous pressure, and it averages out to about 10 or 11 mm

Moore But harking back to your point of a few minutes ago, in shock you have evidence that the coronary bed is not constricted.

Selkurt It is dilated

Moore It seems to me that that is lent additional importance by what you have said, Dr Burton

Burton Yes. I am not, of course, beaten by this because I think that the kidney circulation is very likely a heterogeneous system. In other words, there are two elements which are completely different in their properties and critical closing pressures

Selkurt We were surprised to find this, too

Burton You find this in the mesentery The curve of pressure-flow in the mesentery of the frog is most interesting It shows up these two elements So it might be that the critical closing pressure of the cortex of the kidney had gone very high but the shunt had opened up, and that is the reason a low critical closing pressure is eventually reached

Selkurt That is right

Green Dr Burton picked up the ball before I had a chance to toss a second one to Dr Nickerson, and that is, as far as I know, the heart does not know anything about the peripheral resistance, although it knows the pressure against which it has to eject blood If the arterial pressure is already very low, the heart hasn't much pressure against which to eject the blood, and the arterial shunts particularly improve the ease with which the heart ejects blood

Nickerson That is very true, except that we do not yet have any reliable figures on what happens to the cardiac output immediately after an arterial transfusion There is obviously a factor of improved cardiac activity If there is also a reflex peripheral vasodilatation, the increase in cardiac work, which may be, for example, 25 per cent, is going to bring about a greater increase in peripheral blood flow and tissue oxygenation, although perhaps not as great an increase in blood pressure It is the increased blood flow that is going to improve the condition of the patient or the animal

Stead I just want to say that I think the hearts in eastern North Carolina are smarter than those in western North Carolina I think maybe they do know something about the periphery

Green I would be interested in knowing how they get the information

ADRENAL CORTICOIDS AND SHOCK

Moore I want to make one other point, and that has to do with the adrenal cortex For about two years or so, we have been looking for examples of a shocklike state due to an adrenal cortical insufficiency in surgical patients. We have found very few. One of them I have already told you about, and it is a source of irony to us that we had to anesthetize her twice before we had sense enough to recognize what was going on We have found one or two others, one of whom had unsuspected Addison's disease with bilateral tuberculosis of the adrenals In general, the condition has been rare We have found, as has been reported in the literature, patients with hypothalamic or pituitary lesion with interference with this particular pressor mechanism We have seen patients with myxedema who seem to have an inadequate ability to put out corticoids in response to stress

The problem as we see it at the moment is this in an adrenalectomized animal, or in an Addisonian patient, there is an increased need for corticoids in the presence of practically any sort of stress, including blood loss A patient who is being maintained quite well with one dose of hormone will need twice as much in order to survive even a simple stress like a minor operation So here is point one. that in the absence of normal adrenal function, there is an increased need for replacement hormones when stress occurs

Point two, of course, is the well-known fact that in response to blood loss, or shock, the organism proceeds to put out more corticoids normally. This had been documented in a great many different ways, and I think the evidence is solid, unless you say that in the presence of stress there is a perfectly normal output of corticoids but the metabolic pathway is different so that those same corticoids suddenly have an effect on the electrolyte balance, on eosinophils, on urinary corticoid excretion, and so on, which they previously did not have However, that seems like going far out on a limb to explain it away.

Point three, we have sought, but without luck, an increased destruction of corticoids in the periphery in the presence of damaged tissue Work has been done by Dr Bennett (15) of our group, which I will not quote in detail except to say that it consisted in a measurement of the urinary excretion of steroids after a severe burn in a patient given cortisone Then, a month or two later, when the patient was well, we gave him the same dose of cortisone again We expected to find a greatly increased excretion of steroid in the urine, evidencing that previously the patient was destroying his

Selkurt. In our original data it averaged about 14 mm. Hg We have since repeated that study and corrected for the venous pressure, and it averages out to about 10 or 11 mm

Moore But harking back to your point of a few minutes ago, in shock you have evidence that the coronary bed is not constricted.

Selkurt It is dilated

Moore It seems to me that that is lent additional importance by what you have said, Dr Burton

Burton Yes I am not, of course, beaten by this because I think that the kidney circulation is very likely a heterogeneous system In other words, there are two elements which are completely different in their properties and critical closing pressures

Selkurt We were surprised to find this, too

Burton You find this in the mesentery The curve of pressure-flow in the mesentery of the frog is most interesting It shows up these two elements So it might be that the critical closing pressure of the cortex of the kidney had gone very high but the shunt had opened up, and that is the reason a low critical closing pressure is eventually reached

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cortisone in the damaged tissue We found, to our surprise, quite the contrary, namely, that the excretion was just exactly the same in the well patient So we do not have any solid evidence that this particular hormone is destroyed by damaged tissue or in a diseased organism, and we do not understand the mechanism which increases the requirement for hormones after trauma

The fourth point concerns the site of action of cortisone on the blood vascular tree. We are all aware of the fact that an animal in an Addisonian crisis responds very rapidly to hormone What is the nature of this effect on blood pressure? Is it a change in the permeability of the cells in the vessel walls to water and electrolytes? Why is the vascular tree of an adrenalectomized animal suddenly more effective when hormone is present?

I should like to emphasize again that in acute trauma, in our experience, frank adrenal insufficiency is an extreme rarity But that does not mean that this is still unimportant in our understanding of the response of the organism to shock The traumatized animal apparently stimulates his adrenals to increased activity What good does it do him? It seems to me that that is a very important point

Zweifach We have found it possible to use a histochemical procedure for studying the effects of stagnant hypoxia on different tissues during the progression of shock The compound 2, 3, 5-triphenyl tetrazolium chloride (TTC) is a water soluble, colorless salt, which acts as a hydrogen acceptor and is reduced to a red-colored, insoluble substance by the metabolic activity of cells The metabolic changes which occur in tissues, such as kidney, liver, and adrenal, have been followed in a variety of experimental procedures Especially useful was the application of the TTC technique to a study of adrenal secretory processes (16) The cells of the normal adrenal reduce TTC, which is found to be uniformly deposited throughout the different zones within the intracellular lipid granules It was possible selectively to inhibit the deposition of TTC in the zona glomerulosa with DCA, in the fasciculata with compound E, etc During shock, it was found that the initial hemorrhage rapidly depleted the entire adrenal No deposition of TTC was seen in any of the three zones Shortly thereafter, the glomerulosa began actively to reduce TTC Immediately after transfusion, the entire gland showed a uniform deposition of TTC We therefore assume that the irreversible phase of hemorrhagic shock is not associated with a failure of adrenal secretory activity

Moore That certainly ties in with all the clinical observations

It is secreting well and maybe at an increased rate. Adrenal exhaustion is such a rarity, starting from a normal adrenal, that I am frightened to use the term We have seen patients with prolonged, depleting septic processes who, you would think, had every reason to have their adrenals exhausted, only to find that actually they were putting out pretty good amounts of steroid

Howard. I should like to show you our experiments, done by Dr DeBakey and myself The technique of the shock preparation was very similar to Dr Fine's Two groups of dogs were exposed to the same degree of shock (Figure 23 and Figure 24) Our mortality was 86 per cent for the controls and 82 per cent for the cortisone-treated dogs The latter had at least 100 milligrams daily in addition to the physiologic response

	Number Dogs	Average Time in Shock (minutes)	Hemorrhage per kilogram of Body Wt
Preshock Cortisone	22	127	43 0 ml
No Preshock Cortisone	27	121	44 4 ml

FIGURE 23 Effect of preoperative cortisone on shock pattern Reprinted, by permission, from Howard, J M, and DeBakey, M E The treatment of hemorrhagic shock with cortisone and vitamin B_{12} *Surgery* **30,** *161 (1951)*

	Number Dogs	Died in 48 hrs	
		Number	Percentage
Controls	35	30	86
Cortisone	50	41	82
Vitamin B_{12}	28	23	82

FIGURE 24 Reprinted, by permission, from Howard, J M, and DeBakey, M E The treatment of hemorrhagic shock with cortisone and vitamin B_{12} *Surgery* **30,** *161 (1951)*

Moore Which is just another way of saying that the adrenals of those dogs were doing a pretty good job of giving them an adequate amount of cortisone and that the additional amount did not make any difference

Burch. Your point was that it probably was more effective in producing ruptured peptic ulcers or something of that nature?

Moore. I am sorry if I have given you the impression that I was trying to say it was particularly effective We have looked for patients in whom it might be effective, and in general we have found very few in whom it seemed to be needed.

Zweifach. There is some evidence that the administration of cortisone to animals has a direct effect on peripheral vascular reactivity A rapid return to normal reactivity (within twenty to thirty minutes) occurs in the terminal vascular bed of adrenalectomized rats when cortisone (2 mg per 100 gm) is administered intravenously We have also found that cortisone or ACTH will restore the reactivity of the terminal vascular bed after local mechanical injury or histamine However, we have not been able to improve the hyporeactive character of the circulation during shock by the administration of either cortisone or ACTH.

Moore· That certainly is an interesting problem. Would you go along with this statement that in an animal which is shocked but has intact adrenals to begin with and has a normal pituitary so far as we know, unlimited additional quantities of cortisone have no discernible effect

Zweifach We found no protective action

Stead I am confused by Dr Moore's statement that, in maximal trauma, no further response can be elicited from the adrenals by the use of ACTH We see patients with drug reactions who are fatally ill but who respond to ACTH therapy

Moore I don't think we really disagree at all, Dr Stead, because I have always been careful to say "with maximal trauma," or "with a maximal stimulus" If you take a patient after, say, a subtotal gastrectomy, which we regard as a so-called scale 5, or middling traumatic stimulus, (as evidenced, for example, by his metabolic and adrenal cortical function), and if you give him intravenous ACTH, you will definitely get a response, no matter how slight His electrolyte balance, his corticoid secretions will be changed You have simply defined a big group of patients whose adrenal glands are not working at ceiling values, giving them more ATCH therefore produces a result, since there is still room for further adrenal function

The massive nature of trauma is not always related to an immediate fatal outcome For example, there are few sorts of tissue trauma more massive than an extensive burn, yet it is very rare for burned patients to die in the first few minutes or hours, if there

is no pulmonary component On the other hand, a massive hemorrhage can certainly kill a patient quickly, yet the amount of tissue trauma involved may be small I should therefore like to repeat what I said. In the face of *maximal tissue trauma*, we seem to find that the adrenals cannot be stimulated further by the administration of exogenous ACTH

I should like to say also that in those situations where we have been experimenting with these hormones clinically in acute trauma, we have been inclined to start with cortisone rather than with ACTH, feeling that it was a peripheral tissue that needed more hormones, the adrenals did not need more stimulation

Remington On this adrenal question, I thought we had laid that ghost in the grave ten years ago, the inference being that because an adrenalectomized dog dies of low pressure, therefore there must necessarily be adrenal deficiency in the shock picture in the animal with intact adrenals or the human with intact adrenals It is like the situation with vitamins Because vitamin deficiency is fairly rapidly corrected with vitamins does not mean that I can see better by taking a large dose of vitamin A.

Moore Nobody has said that the normal patient needs more adrenal substances in shock That certainly has not been the burden of my discourse In fact, I have said several times that we have looked hard for evidences of adrenal insufficiency after trauma and we have rarely found it But you cannot lay the ghost of the adrenals in the grave that easily! You cannot get around the fact that without cortisone minor amounts of trauma produce devastating effects on the circulation

Stead I think the fact still remains that, if a man gets hit on the day he comes down with an acute, overwhelming serum sickness, ACTH would be a very useful drug in the treatment of this combined illness

Moore You are dealing with a hypersensitivity reaction primarily.

Remington Adrenal crisis has many differences from shock, as I see it

You spoke of bringing the Addisonian patient out of crisis with salt It is a very hard thing to do You cannot get a dog out of crisis with salt You cannot get a dog out of crisis with transfusion

Moore We all agree with that Adrenal crisis is a very different situation

Remington I think it is just a matter of coincidence that the adrenalectomized dog can stand very little blood loss or trauma without its tripping him into this different pattern of adrenal crisis.

ARTERIAL TRANSFUSIONS

As for arterial transfusion, it is well to remember that blood is a potent dilator Anyone who has used meters will attest to that. Blood is not bland It is a dilator on its first circulation Aren't we merely assuming that venous transfusion is innocuous? A rapid venous transfusion in a normal dog does some drastic things to his circulatory dynamics which I don't understand I have certainly seen the cardiac pattern change quickly and abruptly by driving fluid on the venous side, and driving it not too rapidly at that I thought it was temperature for a long while, but it is more than a temperature effect

Moore. Of course, giving a normal dog or a normal human being a huge overtransfusion is a different problem, because it is easy to push the recipient into pulmonary edema In other words, the right heart takes the transfused fluid and pushes it out into the pulmonary circuit, and then what goes on there, goodness only knows, but the end result is pulmonary edema. In these patients in shock whom we are talking about, the piling up seems to be with forward output of the right ventricle They may later, the next day, go into pulmonary edema I think somebody brought that up, and I mentioned that we had venesected some overtransfused patients the next day.

I go along with your general point that we are much too ignorant of the effects of these unnecessary and excessive venous transfusions Not only may they overload the circulation to the right of the heart, but they also may provide the patient with a lot of unnecessary pigment which his kidneys have to deal with

Sharpey-Schafer We did a lot of transfusions and it was surprising to see how much the young adult heart could stand I think our maximum rate was 3000 ml. of blood at 300 ml a minute That was pretty fast Nothing happened They can stand that quite easily

Moore. But the same thing done to an older patient will kill him

HYPOTENSION ASSOCIATED WITH SPINAL ANESTHESIA

Nickerson Dr Moore raised a question earlier that is of some interest It relates to the hypotension seen in high spinal anesthesia and which may be comparable in many ways to the pink, warm type of shock Regarding the advantages or disadvantages of administering vasoconstrictors in this condition, the available studies on the subject are not adequate, but there is little reason to believe that in the absence of pooling due to the positioning of the patient, there is any significant reduction in cardiac output paralleling the

reduction in blood pressure I have frequently felt that the administration of Neosynephrine or some other vasoconstrictor is really for the benefit of the anesthetist so that he can show on the chart that the blood pressure has not fallen below some figure such as 100/70, rather than for the benefit of the patient Administration of the vasoconstrictor may actually do the patient harm by raising the blood pressure at the expense of the blood flow.

Perhaps Dr Sharpey-Schafer will have something to say about this I understand that in England the administration of vasoconstrictors to patients under spinal anesthesia is much less common than it is in this country

Sharpey-Schafer Our anesthetists don't seem to mind what the blood pressure is They prefer not to be able to measure it

Moore Administration of vasoconstrictors does more than help the anesthetist because you are dealing with a compound situation. It is not just a patient under anesthesia, it is a patient under anesthesia who is undergoing an operation If you take a patient who has maintained himself perfectly well under spinal and turn him on his side, and his pressure goes down and practically disappears, although he may still be warm and pink, you have got to think of the possibility of coronary thrombosis or of cerebral thrombosis I have seen such patients about whom I came to feel a day or two after the operation that, although their skin was nice and warm and pink, their renal cortices were pretty blue and sorry

Bradley We have been studying the effect of spinal anesthesia on the circulatory system for a long time, and we are convinced that if a patient under spinal anesthesia is not traumatized or moved about in any way, the blood pressure will not fall We believe that the fall in blood pressure usually indicates a change of some detrimental character, although the disturbance, such as a shift in position, may be very minor indeed

We have seen a number of patients in whom the blood pressure falls markedly during the course of anesthesia, in association with a marked drop in renal blood flow In these patients the administration of Neosynephrine or Noradrenalin causes a rise in the renal blood flow as the blood pressure comes up, which is quite out of keeping, of course, with the normal action of the drug in a patient who is not anesthetized I don't want to leave the impression, however, that Noradrenalin, if given to a patient with spinal anesthesia whose blood pressure is not falling, will cause a rise in renal blood flow It does not There seems to be some kind of critical point at which Noradrenalin will simply cause a rise in blood pres-

sure without further increase in renal blood flow

Shorr: I am wondering how long one waits, if the patient's blood pressure is unmeasurable, before deciding whether or not to use Neosynephrine

Nickerson. When a threatening nidus of thrombus formation is present, the rate, as distinct from the volume of flow, becomes quite important, particularly in the coronaries Under other conditions, the myocardium does not suffer from a decreased blood pressure It has been shown that the work required of the heart actually decreased faster than the coronary blood flow during hypotension (17)

A second matter is the relationship of positional factors to the hypotension of spinal anesthesia When the venous return is impaired, either because of the over-all position of the patient or because of pressure on a central vein, we have, of course, quite a different picture

Finally, in answer to Dr Shorr's question, regarding how long one would want to follow a patient with an unobtainable blood pressure, I think few of us would want to go very long without being able to obtain a blood pressure reading The waiting would activate our own sympathetic system, if not the patient's The real question is whether the administration of a vasoconstrictor, which will constrict the arterioles and raise the blood pressure by preventing the blood from flowing as readily through various organs, is the method of choice for raising the pressure

Shorr This reasoning would seem to lead to the conclusion that it would actually be harmful to restore a normal blood pressure by the use of such agents as Neosynephrine I wonder how justifiable this point of view is?

Nickerson I think it all depends upon the hemodynamic situation We know that a vasoconstrictor can kill an animal which would otherwise survive a borderline hemorrhage

Shorr· I agree that it is possible that an exaggerated vasoconstriction could be obtained which would be harmful, but I wonder how often this is likely to occur in the situation we have been discussing We frequently encounter these acute episodes when the blood pressure is unmeasurable by the cuff method, and this may be the case after removal of pheochromocytoma or after adrenalectomy as in Cushing's disease In such patients during operation we have so far never encountered any instance in which the restoration to normotensive levels was associated with any harmful effects

Nickerson The discouraging thing about trying really to settle

this question is the fact that it is essentially impossible to obtain a series of cases in which alternate patients received or did not receive a vasoconstrictor Anesthetists who feel that vasoconstrictors are desirable will give them to all cases which appear to be in trouble, the ones who feel that these agents are not necessary or are harmful will not give them to any I think we cannot show that patients treated by the English anesthesiologists suffer because they are followed without the administration of vasoconstrictors This question at the moment is a matter of argument rather than of fact because, unfortunately, adequate data are not available

Haley Doesn't Phillips in Philadelphia have such data on a large number of cases?

Nickerson No, he has data on the ability of the various vasoconstrictors to raise the blood pressure and on the smoothness of maintaining that blood pressure, comparing one drug against the other I do not believe he has data regarding the effects of administering or withholding vasoconstrictors on the ultimate result of treatment

Howarth. Some English anesthetists, far from administering vasoconstrictors to maintain the blood pressure, have been giving penta- and hexa-methonium to reduce it further and obtain a bloodless field One group with this purpose in mind has actually venesected cases before operation

Howard Would you feel the same way about the hypertensive patient? Do you think the incidence of complications would be any different in a hypertensive given a spinal anesthesia, with a low blood pressure resulting from it, or in the patient who has had bilateral sympathectomy for hypertension and whose pressure will drop completely out of sight unless it is supported?

Nickerson There is no argument about the fact that more rapid and greater falls in pressure occur in hypertensive patients I do not know of any data to indicate that more harm has been done these patients by that fall Perhaps others could shed more light on this question

Bradley Drs Griffiths and Gillies (18) at the Royal Infirmary in Edinburgh are recommending the use of high spinal anesthesia during sympathectomy in patients with hypertensive disease They claim that the prolonged hypotensive state resulting from this procedure has no detrimental effects and may indeed lessen the hazard of hemorrhage I am frequently amazed at the ease with which patients, formerly hypertensive, adjust to normotensive levels after sympathectomy These responses appear to indicate that elevated

blood pressure is not necessary for adequate perfusion of vital vascular beds in these patients In any case, of course, I should think that a lowered blood pressure might prove dangerous in the face of critical reduction of coronary blood flow secondary to coronary arteriosclerosis

Howard I do not know of any anesthetists who recommend spinal anesthesia for the hypertensive patient

Stead It is certainly surprising how many times you can maintain hypotension without getting into trouble In persons with coronary artery disease and cerebral arteriosclerosis, accidents do occur

Shorr I should like briefly to cite our own experiences with patients with pheochromocytoma The surgeons at our hospital are prone not to give pressor agents when the hypotensive episodes occur in these patients postoperatively On our part we are prone to use pressor agents In one instance which we treated jointly with our surgical staff, the blood pressure fell postoperatively to alarmingly low levels, apparently due to a progressive expansion of the vascular bed following removal of the tumor We used pressor agents, both epinephrine and Neosynephrine, gradually tapering off the rate of administration until, after about forty-eight hours, the blood pressure was maintained without this help This patient had a marked hemodilution, and only after we approximated the blood volume to the expanding vascular bed by blood transfusions were we able successfully to wean her from the necessity of support by pressor agents In a second case, we decided not to use pressor agents, but to keep up with the expansion of the vascular tree by transfusions As the bed gradually accommodated itself to the lessened epinephrine output, hypertension redeveloped and the patient had to be bled to just about the same extent as he had been previously transfused We all felt that we had more trouble with the latter procedure than when we continued to support the patient with pressor agents Apparently, we must keep in mind the expanding vascular bed after removal of a pheochromocytoma and try to cope with it and to prevent the blood pressure from falling to such low levels as to jeopardize the circulation and possibly the integrity of certain organs, such as the kidney On the other hand, we have also encountered patients who require no support whatever after removal of the pheochromocytoma The question is, do we do any harm in maintaining normotensive levels with pressor agents in this type of patient, and, if not, should we frown on such measures when severe hypotension does develop?

Nickerson· No generalization will apply to every case

Shorr Well, it seems as though we are still eager to go on, but a healthy weariness should tell us to stop Speaking for myself, this has been a provocative and illuminating two-day discussion. I know that it would be your wish that I express to Dr Fremont-Smith and to the Josiah Macy, Jr Foundation our thanks and deep appreciation for this opportunity, and for the others to come

Fremont-Smith Thank you very much We are grateful to all of you for coming and for helping us with this experiment in communication

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